Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS201964-0001
Title	A Multicenter, Open-Label, Dose Escalation Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and the Food Effect on Pharmacokinetics of the DNA-PK Inhibitor M3814 in Combination with Avelumab with and without Palliative Radiotherapy in Participants with Selected Advanced Solid Tumors
Study Phase	Phase I
Investigational Medicinal Product(s)	MSB0010718C (avelumab), MSC2490484A (M3814)
Clinical Study Protocol Version	26 June 2019/Version 2.0
Integrated Analysis Plan Author	Coordinating Author Biostatistics, Merck Healthcare KGaA PPD PPD Merck Healthcare KGaA
Integrated Analysis Plan Date and Version	05 November 2020 / Version 1.0
Integrated Analysis Plan Reviewers	Function / Name CCI

Approval Page

Integrated Analysis Plan: MS201964-0001

A Multicenter, Open-Label, Dose Escalation Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and the Food Effect on Pharmacokinetics of the DNA-PK Inhibitor M3814 in Combination with Avelumab with and without Palliative Radiotherapy in Participants with Selected Advanced Solid Tumors

Approval of the IAP by all Merck Healthcare KGaA Data Analysis Responsible has to be documented within ELDORADO via eSignature. With the approval, the Merck Healthcare KGaA responsible for each of the analysis 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	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
BOR	Best Overall Response
ATC	Anatomical Therapeutic Chemical classification
C_{EOI}	Observed concentration at the end of infusion period
CI	Confidence Interval
C_{max}	Maximum Observed Concentration
COVID-19	Coronavirus Disease 2019
CR	Complete Response
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
C_{trough}	Concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing)
CV	Coefficient of Variation
DLT	Dose Limiting Toxicity
CCI	[redacted]
DOR	Duration of Response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
FAS	Full Analysis Set
FE	Food Effect
GeoCV	Geometric Coefficient of Variation
GeoMean	Geometric Mean
IAP	Integrated Analysis Plan
irAE	Immune Related Adverse Event
IPD	Important Protocol Deviation
IRR	Infusion-Related Reaction
LLN	Lower Limit of Normal

LLOQ	Lower Limit of Quantification
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MTD	Maximum Tolerated Dose
NE	Not Evaluable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
ORR	Objective Response Rate
OS	Overall Survival
CCI	[redacted]
PD	Progressive Disease
CCI	[redacted]
[redacted]	[redacted]
PFS	Progression-Free Survival
CCI	[redacted]
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase II Dose
RT	Radiotherapy
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SCR	Screening Analysis Set
SD	Stable Disease
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
StDev	Standard Deviation
SOC	System Organ Class
T4	Thyroxine
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time to Maximum Concentration

TSH	Thyroid-stimulating hormone
ULN	Upper Limit of Normal
WHO	World Health Organization

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	05 Nov 2020	PPD	N/A – First version

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the final analysis of data collected for Parts A, B, and FE (Food Effect) of the Clinical Trial Protocol MS201964-0001. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR) after study completion/database lock. Additionally, the planned analyses identified in this IAP will be included in regulatory submissions or future manuscripts. Any post-hoc or unplanned analyses performed and included in the CSR, but not identified in this prospective IAP, will be clearly identified as such in the CSR.

The IAP is based on Section 9 (*Statistical Considerations*) of the study protocol and is prepared in compliance with ICH E9.

Details on outputs used to support review of the study by a Safety Monitoring Committee (SMC) are available in the SMC Charter.

5 Objectives and Endpoints

Part A:

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
To determine a safe, tolerable, RP2D and/or the MTD of M3814 when given in combination with avelumab	• Occurrence of dose limiting toxicities (DLTs)	15.1
Secondary		
To evaluate the safety profile and tolerability of M3814 in combination with avelumab.	• Occurrence of treatment-emergent adverse events and treatment-related adverse events according to the NCI-CTCAE v 5.0, and serious adverse events • Occurrence of abnormalities (Grade ≥ 3) in laboratory test values, markedly abnormal vital sign measurements, markedly abnormal physical examination measurements, clinically significant abnormal ECG, marked changes in ECOG PS	15.2 – 15.6
To characterize the pharmacokinetics of M3814 and avelumab when given as combination therapy.	• Pharmacokinetic profile of avelumab in terms of pharmacokinetic parameter estimates, as feasible (eg, C_{max}, C_{min}, Racc[C_{max}], Racc[AUC] and $t_{1/2}$) • Pharmacokinetic profile of M3814 in terms of pharmacokinetic parameter estimates (C_{max}, t_{max}, C_{min}, C_{avg}, fluctuation index, AUC_{0-t}, $AUC_{0-\infty}$, $R_{acc}[C_{max}]$, $R_{acc}[AUC]$, $t_{1/2}$, Vz/f, CL/f, and Λ_z)	16.1
To evaluate the immunogenicity of avelumab in combination with M3814.	• Immunogenicity as measured by ADA	16.3
To evaluate the preliminary antitumor activity of M3814 when given in combination with avelumab in participants with locally advanced or advanced solid tumors.	• Confirmed BOR according to RECIST v 1.1, as assessed by the Investigator	14.1
	• Confirmed DOR according to RECIST v 1.1, as assessed by the Investigator	14.2
	• PFS time according to RECIST v 1.1, as assessed by the Investigator	14.4
	• Tumor size measurement based on Investigator assessment according to RECIST v 1.1	14.3
	• Overall Survival	14.5
CCI		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Objectives	Endpoints (Outcome Measures)	IAP section
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Part B:

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
To determine a safe, tolerable, RP2D and/or the MTD of M3814 when given in combination with avelumab and radiotherapy.	• Occurrence of DLTs	15.1
Secondary		
To evaluate the safety profile and tolerability of M3814 in combination with avelumab and radiotherapy.	• Occurrence of treatment-emergent adverse events and treatment-related adverse events according to the NCI-CTCAE v 5.0, and serious adverse events • Occurrence of abnormalities (Grade ≥ 3) in laboratory test values, markedly abnormal vital sign measurements, markedly abnormal physical examination measurements, clinically significant abnormal ECG, marked changes in ECOG PS • Incidence, severity and outcomes of RT-induced toxicity	15.2 – 15.6
To characterize the pharmacokinetics of M3814 and avelumab when given in combination with radiotherapy.	• Pharmacokinetic profile of avelumab in terms of pharmacokinetic parameter estimates, as feasible (eg, C_{max}, Cmin, Racc[C_{max}], Racc[AUC] and $t_{1/2}$) • Pharmacokinetic profile of M3814 in terms of pharmacokinetic parameter estimates (C_{max}, tmax, C_{min}, C_{avg}, fluctuation index, AUC_{0-t}, $AUC_{0-\infty}$, Racc[C_{max}], Racc[AUC], $t_{1/2}$, Vz/f, CL/f, and Λ_z)	16.1
To evaluate the immunogenicity of avelumab in combination with M3814 plus radiotherapy.	• Immunogenicity as measured by ADA	16.3
To evaluate the preliminary antitumor activity of M3814 when given in combination with avelumab and radiotherapy in participants with	• Confirmed BOR according to RECIST v 1.1, as assessed by the Investigator	14.1
	• Confirmed DOR according to RECIST v 1.1, as assessed by the Investigator	14.2

Objectives	Endpoints (Outcome Measures)	IAP section
locally advanced and advanced solid tumors	• PFS time according to RECIST v 1.1, as assessed by the Investigator	14.4
	• Tumor size measurement based on Investigator assessment according to RECIST v 1.1	14.3
	• Overall Survival	14.5
CCI		
[redacted]		

Part FE:

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
To determine and compare the pharmacokinetic profile of M3814 under fasted and fed conditions	Area under the M3814 plasma concentration-time curve (AUC) from time zero to the last quantifiable sampling time (AUC_{0-t}), and maximum M3814 plasma concentration observed (C_{max}).	16.1
Secondary		

Objectives	Endpoints (Outcome Measures)	IAP section
To evaluate the safety profile and tolerability of M3814 in combination with avelumab under fasted and fed conditions	• Occurrence of treatment-emergent adverse events and treatment-related adverse events according to the NCI-CTCAE v 5.0, and serious adverse events • Occurrence of abnormalities (Grade ≥ 3) in laboratory test values, markedly abnormal vital sign measurements, markedly abnormal physical examination measurements, clinically significant abnormal ECG, marked changes in ECOG PS	15.2 – 15.6
To evaluate the immunogenicity of avelumab in combination with M3814	• Immunogenicity as measured by ADA	16.3
To evaluate the preliminary antitumor activity of M3814 when given in combination with avelumab and radiotherapy in participants with locally advanced and advanced solid tumors	• Confirmed BOR according to RECIST v 1.1, as assessed by the Investigator	14.1
	• Confirmed DOR according to RECIST v 1.1, as assessed by the Investigator	14.2
	• PFS time according to RECIST v 1.1, as assessed by the Investigator	14.4
	• Tumor size measurement based on Investigator assessment according to RECIST v 1.1	14.3
CCI [redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Objectives	Endpoints (Outcome Measures)	IAP section
CCI [redacted]	[redacted]	[redacted]

6 Overview of Planned Analyses

This IAP covers the analyses for efficacy and safety based on the data cut-off date for the final analysis; in addition, this IAP describes the interim safety analyses to be conducted for each study part, as well as an interim efficacy analysis for Part A or B, whichever is completed first. Statistical analyses will be performed using cleaned electronic case report form (eCRF) data as well as data collected by external vendors, including CCI [redacted] pharmacokinetics (PK) data, CCI [redacted] and immunogenicity data. All data will be included up to a clinical cut-off date which will be determined as described in the sections below.

A data review meeting will be held prior to database lock. In addition, no database can be locked until this IAP has been approved.

In addition to the analyses described in the following sections, an SMC will review the safety and any available PK/Pd data of participants enrolled in any part of the study on a regular basis. During Part A and Part B, the SMC will decide on relevant dose limiting toxicities (DLTs) (Protocol Section 6.6.3) based on protocol criteria. The SMC will decide by consensus on dose escalation or de-escalation of M3814, or suspension of enrollment and/or declaration of the maximum safe dose (i.e., maximum tolerated dose, MTD) and the Recommended Phase II Dose (RP2D) of M3814 in combination with avelumab (Part A) and with avelumab and radiotherapy (RT) (Part B). CCI [redacted]

6.1 Interim Analyses

Two interim safety analyses, one each for Part A and Part B, are planned. The interim safety analyses will be limited in scope and will include a subset of the safety analyses described in this IAP. Each interim safety analysis will be conducted after the RP2D for the given study part is selected. The DLT period for Part A is defined as the first 3 weeks (21 days) of the study, following the start of the study intervention. The DLT period for Part B is defined as the first 4 weeks (28 days) of the study, following the start of study intervention. The interim safety analyses will be conducted in addition to regularly planned SMC meetings.

One interim efficacy analysis for Part A is planned. The interim efficacy analysis will be limited in scope and will include a subset of the efficacy analyses described in this IAP. This analysis will be conducted after all subjects in Part A are either no longer actively participating in the study, or would be assumed to have completed at least two post-baseline tumor assessments if still enrolled in the study (i.e., completed the protocol-specified assessment at the Day 112 study visit). Although it is not anticipated that Part B would be completed prior to Part A, the interim efficacy analysis would be for Part B *instead of* Part A if that scenario were to occur.

As all analyses in this study are considered exploratory, no formal adjustment for multiplicity will be undertaken to account for this interim efficacy analysis.

6.2 Final Analysis

The Final Analysis of the study will include all analyses described in this IAP and will include data from participants in Part A, Part B, and Part FE. Each study part will be presented in a separate set of outputs, with separate columns for each dose level.

All final, planned analyses for the CSR that are identified in the Clinical Trial Protocol and in this IAP will be performed only after the study ends. The study will end when 1 year has passed from the day the last participant in any of the three study parts has received the last dose of study intervention or all participants are no longer actively participating in the study, whichever comes first.

A data review meeting will be held prior to database lock for any analysis. In addition, no database can be locked and until this IAP has been approved.

7 Changes to the Planned Analyses in the Clinical Study Protocol

The statistical methods as described in the protocol were adopted. The following changes to the planned analyses were made.

M3814 and M3814 metabolite (*0*-demethylated product M467) pharmacokinetic parameters listed in protocol no longer to be calculated

AUC_{0-t}	Area under the concentration-time curve (AUC) from time of dosing to the time of the last observation
$AUC_{0-\infty}$	AUC from time of dosing to infinity
C_{min}	Minimum concentration observed postdose
C_{avg}	Average concentration at steady state
CL/f	Oral clearance
V_z/f	Apparent volume of distribution
Fluctuation index	Fluctuation between maximum and minimum concentrations

Please refer to Section 16.1 for a complete list of PK parameters which will be reported.

8 Protocol Deviations and Analysis Populations

8.1 Definition of Protocol Deviations and Analysis Populations

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

Important protocol deviations include, but are not limited to:

- Participants being enrolled in the study despite not satisfying the inclusion/exclusion criteria;
- Participants developing withdrawal criteria while on the study but not being withdrawn;
- Participants receiving the incorrect dose of study treatment;
- Participants receiving an excluded concomitant medication;
- Participants failing to complete visits/study activities outlined in the Schedule of Assessments without an approved reason;
- Deviations from GCP.

A complete list of protocol deviations prospectively defined for this study is available in the Protocol Deviation Guidance document. All IPDs will be documented in the Clinical Trial Management System (CTMS) and in the Study Data Tabulation Model (SDTM) datasets, whether identified through site monitoring, medical review, or data management programming.

Protocol deviations attributed to the impact of the novel coronavirus disease (COVID-19) pandemic will be labeled accordingly. Both important and non-important protocol deviations attributable to the COVID-19 pandemic will be included in the SDTM datasets.

Please refer to Section 10.3 for details on reporting of protocol deviations.

8.2 Definition of Analysis Populations and Subgroups

Unless otherwise specified, participants will be analyzed according to the treatment group/cohort assigned at screening.

Screening Analysis Set (SCR)

The Screening Analysis Set includes all participants who signed the informed consent form.

Full Analysis Set (FAS)/Safety (SAF) Analysis Set

The FAS/SAF Analysis Set includes all participants who received at least one non-zero dose of any study intervention. Study intervention includes avelumab, M3814, and in the case of participants in Part B, RT.

Dose Limiting Toxicity (DLT) Analysis Set

The DLT Analysis Set is defined for the dose-escalation Parts A and B and includes all participants who are DLT evaluable. This population is not defined for Part FE.

- **Part A:** The DLT Analysis Set includes all participants who have received at least 34 of 42 daily doses of M3814, 2 administrations of avelumab, and complete the DLT period. Additionally, participants treated in dose escalation cohorts who experience a DLT during the DLT period, regardless of the amount of study intervention received or completion of the DLT period are included.

  For Part A, the DLT period is defined as the first 3 weeks (21 days) of the study, following the start of any study intervention.

- **Part B**: The DLT Analysis Set includes all participants who have received at least 8 of 10 daily doses of M3814 and 3 administrations of avelumab and 8 fractions of RT and complete the DLT period. Additionally, participants treated in dose escalation cohorts who experience a DLT during the DLT period, regardless of the amount of study intervention received or completion of the DLT period are included.

  For Part B, the DLT period is defined as the first 4 weeks (28 days) of the study, following the start of any study intervention.

Pharmacokinetic (PK) Analysis Set

The PK Analysis Set is defined separately for Parts A/FE and B.

- **Part A** and **Part FE**: The PK Analysis Set includes all participants who complete 1 administration of M3814 and avelumab starting on Day 1 and who provide at least 1 post-dose sample with measurable concentrations of M3814.

- **Part B:** The PK Analysis Set includes all participants who have received at least the first dose of M3814 and who provide at least 1 post-dose sample with measurable concentrations of M3814.

CCI [redacted]

[redacted]

Immunogenicity (ADA) Analysis Set

The ADA Analysis Set includes all participants who complete at least one administration of both M3814 and avelumab and have at least one valid ADA result.

Table 1: Summary of Analyses and Associated Analysis Sets

Analyses	SCR	SAF	FAS	DLT	PK	M3814-BM-Pd	BM-Tu	BM-IP	BM-Pd	PGt	ADA
Disposition	✓										
Baseline Assessments		✓									
Previous and Concomitant Therapies		✓									
Compliance and Exposure		✓									
Efficacy			✓								
Safety: DLTs and MTD/ RP2D				✓							
Other Safety and Tolerability		✓									
Pharmacokinetic Analysis					✓						
[redacted]						■					
[redacted]							■				
[redacted]								■			
[redacted]									■		
[redacted]										■	
Immunogenicity (ADA) Analysis											✓

9 General Specifications for Data Analyses

Unless otherwise indicated, summary tables will be presented separately for each study part, by dose level and overall, based on the analysis set of interest; listings will be presented using the same analysis sets as the corresponding tables. Data from the three separate study parts will not be aggregated for any analyses.

9.1 General Specifications and Definitions for Analysis

Pooling of centers

Data will be pooled across centers.

Data handling after interim analysis cut-off date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses, or imputations. For example, laboratory values of samples taken after data cut-off, adverse events (AEs) with onset date after data cut-off, etc. will not be included in any analysis or listing. Stop dates, however, are not affected by this rule – e.g. if an AE starts prior to the cut-off, but stops after date of cut-off, the AE end date will be included in listings.

Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics i.e., number of subjects considered and number of missing values, [i.e., n (missing)], mean, median, standard deviation (StDev), minimum, maximum and first and third quartile (Q1 and Q3). As per general reporting conventions, mean, median, Q1, and Q3 will be displayed with one more decimal place than the raw data; StDev will be displayed using two more decimal places than the raw data. Percentages will be reported to one decimal place. Rounding will be performed to closest integer/decimal using the common mid-point between the two consecutive values – e.g., 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated, the calculation of proportions/percentages for a given qualitative variable will include subjects with missing values in the denominator. When applicable, counts of missing observations for a qualitative variable will be presented on summary tables.

Unless otherwise specified, percentages will be based on the number of subjects in the analysis set used for the given summary.

For presentation of PK results please refer to Section 9.2.

Definition of baseline

In general, the last non-missing measurement prior to the first study intervention will serve as the baseline measurement. Study intervention includes avelumab, M3814, and in the case of participants in Part B, RT. If the time of an assessment and/or the time of the initial dosing are unknown and dosing date and assessment date are the same, the following rule is used: assessments intended to be completed prior to dosing, as per protocol, and completed on scheduled visits are assumed to have been performed prior to dosing and may be selected as baseline; assessments completed on unscheduled visits are assumed to have been performed after dosing and are not eligible for selection as baseline. Unscheduled assessments which occur unambiguously prior to the start of any study intervention are eligible for selection as baseline.

Definition of change from baseline

Change from baseline = visit value – baseline value

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

Significance level

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

Conversion factors

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

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

Details for determination of participant age and body mass index (BMI) are given in Section 11.1.

Definition of duration

Duration will be calculated by the difference of start and stop date + 1. For example, AE duration (days) = AE end date – AE start date + 1

Unless otherwise specified, the time since an event will be calculated as reference date minus date of event. For example, time since last dose date will be calculated as the event date – the date of last dose.

Definition of treatment day

Treatment day is defined relative to the date of first dose of any study intervention. Study intervention includes avelumab, M3814, and in the case of participants in Part B, RT. Day 1 represents the first day of treatment; the day before is defined as Day -1 (no 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 the minimum of (last date of study intervention + 30 days, start day of new anti-cancer drug therapy – 1 day, death).

Scheduled and unscheduled visits

Assessments from unscheduled visits will be considered for the derivation of baseline values and worst on-treatment values and grades; they will also be included in listings. Please see Section 9.3 for details on visit windowing.

Software

All analyses will be performed using SAS® Software version 9.4 or higher, with the exception of M3814 and M467 PK parameters which will be derived using noncompartmental methods with the validated computer program Phoenix® WinNonlin® 8.0 or higher (Certara, L.P., Princeton, New Jersey, USA).

9.2 Presentation of Pharmacokinetic Results

9.2.1 Presentation of Pharmacokinetic Concentration Data

M3814, *0*-demethylated product M467 (if available), and avelumab concentration data will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (StDev), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max). In cases with $n \leq 2$, only n, Min, and Max will be reported.

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

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

9.2.2 Presentation of Pharmacokinetic Parameter Data

Pharmacokinetic parameter data will be descriptively summarized using: n, Mean, StDev, CV%, Min, Median, Max, geometric mean (GeoMean), and the geometric coefficient of variation (GeoCV). For time to reach maximum observed concentration (t_{max}), only n, Min, Median, and Max will be reported. In cases with $n \leq 2$, only n, Min, and Max will be reported. The PK parameter maximum observed plasma concentration (C_{max}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the 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:	3 Significant digits
StDev:	4 Significant digits
CV%, GeoCV%:	1 decimal place

9.2.3 Visit Windowing

The assignment of visit windows is described in Table 2 and Table 3 for Part A and Part FE subjects, and Table 4 and Table 5 for Part B subjects for the purpose of by-visit analyses of laboratory assessments, vital signs (VS), and electrocardiogram (ECG) data. In addition to those tables, the following rules will be used for assignment of visits:

- Baseline will be derived as described in Section 9.1.
- Both scheduled and unscheduled assessments are considered in visit windowing.
- No visit windowing will be performed at End-of-Treatment, Safety Follow-up, or Long-Term Follow-up visits. Instead, the earliest non-missing observation among the unscheduled or scheduled assessments for each visit will be used.
- If there are multiple assessments for any specified visit and some of them are from scheduled visits with non-missing assessment results, the assessment from scheduled visit that is closest to the planned study day will be used for analysis. If two scheduled visits are equally spaced around the assigned study day, the earlier of the two will be used.
- If there are multiple assessments for any specified visit and none of them are from scheduled visits, the assessment with non-missing results and closest to the planned study day will be used.
- If there are two or more unscheduled assessments with non-missing results and the same distance to the planned study day, the assessment prior to the planned study day will be used in deriving visit window. For example, if the lab assessment was done on both Study Day -1 and 1, then the assessment on Study Day -1 will be used for visit windowing.

Table 2: Visit Window Definition for Lab Assessments for Part A & FE Participants

Assigned Study Day (Inclusive)		Planned Study Day (AWTARGET)	Analysis Visit (N) (AVISITN)	Analysis Visit (AVISIT)
From (AWLO)	To (AWHI)			
-28	-1	-1	100	Screening
~	1		1	Baseline
1	4	1	101	Visit 1 Day 1
5	25	22	103	Visit 3 Day 22
26	32	29	104	Visit 4 Day 29
33	60	57	106	Visit 6 Day 57
61	88	85	108	Visit 8 Day 85
Further lab visits are scheduled for even visit numbers (X = 12, 14, …), and the following algorithm can be applied:				
Y-24	Y+3	Y = (X-2) * 14 + 1	100+X	Visit X Day Y

Table 3: Visit Window Definition for Vital Sign & ECG Assessments for Part A & FE Participants

Assigned Study Day (Inclusive)		Planned Study Day (AWTARGET)	Analysis Visit (N) (AVISITN)	Analysis Visit (AVISIT)
From (AWLO)	To (AWHI)			
-28	-1	-1	100	Screening*
~	1		1	Baseline*
1	4	1	101	Visit 1 Day 1*
5	18	15	102	Visit 2 Day 15*
19	25	22	103	Visit 3 Day 22*
26	32	29	104	Visit 4 Day 29
33	46	43	105	Visit 5 Day 43
47	60	57	106	Visit 6 Day 57
61	74	71	107	Visit 7 Day 71
75	88	85	108	Visit 8 Day 85
* Visit also includes ECG assessment. Further vital sign assessments are scheduled at each biweekly visit, and the following algorithm can be applied:				
Y-10	Y+3	Y = (X-2) * 14 + 1	100+X	Visit X Day Y

Table 4: Visit Window Definition for Lab Assessments for Part B Participants

Assigned Study Day (Inclusive)		Planned Study Day (AWTARGET)	Analysis Visit (N) (AVISITN)	Analysis Visit (AVISIT)
From (AWLO)	To (AWHI)			
-35	-1	-1	100	Screening
~	1		1	Baseline
1	1	1	202	Part B Visit 2 Day 1
2	7	5	206	Part B Visit 6 Day 5
8	15	12	211	Part B Visit 11 Day 12
16	43	29	213	Part B Visit 13 Day 29

Table 5: Visit Window Definition for Vital Sign & ECG Assessments for Part B Participants

Assigned Study Day (Inclusive)		Planned Study Day (AWTARGET)	Analysis Visit (N) (AVISITN)	Analysis Visit (AVISIT)
From (AWLO)	To (AWHI)			
-35	-1	-1	200	Screening
~	1		1	Baseline
1	1	1	202	Part B Visit 2 Day 1*
2	2	2	203	Part B Visit 3 Day 2
3	3	3	204	Part B Visit 4 Day 3
4	4	4	205	Part B Visit 5 Day 4
5	5	5	206	Part B Visit 6 Day 5
8	8	8	207	Part B Visit 7 Day 8
9	9	9	208	Part B Visit 8 Day 9
10	10	10	209	Part B Visit 9 Day 10
11	11	11	210	Part B Visit 10 Day 11
12	13	12	211	Part B Visit 11 Day 12
14	16	15	212	Part B Visit 12 Day 15
17	30	29	213	Part B Visit 13 Day 29*
* Visit also includes ECG assessment.				

9.3 Handling of Missing Data and Imputation Rules

Handling of missing data:

Unless otherwise specified, missing data will not be replaced.

In all participant data listings, imputed values will be presented and flagged as such.

Missing statistics, e.g., when they cannot be calculated, should be presented as "nd" (not done). For example, if n=1, the measure of variability (StDev) cannot be computed and will be presented as "nd".

Unless otherwise specified, the number of subjects counted as "missing" is the number of participants in the relevant analysis population minus the number of non-missing results for the given analysis.

Handling of missing data for PK parameter calculations is discussed under Section 16.1.

Laboratory data outside the limit of quantitation

For laboratory assessments indicating that the sample tested below the lower limit of quantitation (LLOQ) for the analyte in question, half the lower limit of quantitation (½*LLOQ) will be used as the analysis value. For laboratory assessments testing above the upper limit of quantitation (ULOQ), the analysis value will be imputed as {ULOQ + 1*(the level of precision of ULOQ)}. For example, if an assessment tests at a value ">7.0", the level of precision is 0.1 and the analysis value will be 7.1. The imputed analysis values will be used in all analyses (e.g., summary statistics) and will be used for determination of toxicity grading. Listings will present the standardized unit values as provided in the raw data, indicating the assessment value was not quantifiable (e.g., ">7.0").

Partial dates will be imputed as follows:

Disease history

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

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

Adverse Events

Incomplete AE-related dates will be imputed as follows:

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

Prior/Concomitant Medication

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

- If the medication date is missing completely, then the medication date will be replaced by the start date of the first study intervention.
- If the day of medication date is missing, but the month and year are equal to the start date of the first study intervention, then the medication date will be replaced by the start date of the first study intervention. For example, if the medication start date is --/JAN/2015, and study intervention start date is 15/JAN/2015, then the imputed medication start date will be 15/JAN2015.
- If both the day and month of medication start date are missing but the start year is equal to the start date of the first study intervention, then the medication date will be replaced by the start date of the first study intervention. For example, if the medication start date is --/---/2014, and study intervention 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 month will be replaced by 1.
- In the case that the imputed start date occurs after the medication end date, the medication end date will be used as the start date.

- Incomplete end 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 end date.
- In all other cases, the incomplete medication end date will not be imputed.

Subsequent Anti-Cancer Therapy

Incomplete dates for start date of subsequent anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period.

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, and the date of subsequent anti-cancer therapy will not be used for any calculations.

Exposure

For each treatment component, in case the last administration date is incomplete, the date of last administration of study intervention will be taken from the "Treatment Termination" eCRF pages.

Date of Last Contact

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

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

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

Death date

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

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

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

Tumor assessments

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

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

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

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

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

10 Study Participants

10.1 Disposition of Participants and Discontinuations

Analysis set: Screening

The following information will be summarized by dose level and overall within each study part:

- Number of participants screened
- Number of participants who discontinued the study prior to study intervention, and by reason (e.g., subject did not meet all eligibility criteria, withdrew informed consent, died prior to receiving treatment)
- Number of participants who received at least one dose of any study intervention
- Number and percentage of participants with at least one study intervention ongoing
- Number and percentage of participants who received at least one dose of study intervention, displayed by specific study intervention component
- Number and percentage of participants with study intervention ongoing, displayed by specific study intervention component
- Number and percentage of participants who discontinued study intervention, overall and by reason, displayed by specific study intervention component
- Number and percentage of participants who discontinued all study intervention, overall and by main reason (reason for discontinuation of last study intervention)
- Number and percentage of participants who re-initiated study intervention
- Number and percentage of participants who discontinued study intervention after re-initiation, overall and by primary reason, displayed by specific study intervention component
- Number and percentage of participants who received subsequent anti-cancer therapy
- Number of participants who discontinued the study and main reason

The number and percentage of participants in each of the above disposition categories will be presented by assigned study intervention group and overall. Percentages will be presented with respect to the number of SAF Analysis Set participants.

The number of participants in the analysis populations outlined in Section 8.2 will be summarized by study intervention group and by site.

The number and percentage of participants enrolled by region and by country within region will be summarized.

All relevant participant disposition data will be presented in data listings.

10.2 COVID-19 Impact

No changes to the per-protocol planned analyses of safety or efficacy endpoints will be made due to the impact of coronavirus disease 2019 (COVID-19) outbreak.

Additional outputs (summary table and listing) will be generated in order to describe and quantify the impact of COVID-19 pandemic on the following parameters:

- Subjects potentially affected by COVID-19
- Adverse Events
- Protocol deviations (important and non-important)
- Missed Visits
- Missed efficacy evaluations
- Tele-Visits performed
- Drug Administration: missed doses
- Drug Administration: dose delays
- Treatment Discontinuation
- Study Discontinuation
- Death

Potentially affected subjects are defined as:

a) Patients who started treatment after start of the COVID-19 pandemic, or
b) Patients who started treatment prior to start of the COVID-19 pandemic and are still ongoing after the start of the pandemic.

The start of COVID-19 pandemic will be defined by country as the earliest date of either: (1) the date of the first death attributed to COVID-19 in the patient's country, according to the published data by European Centre for Disease Prevention and Control on 26th June 2020 or (2) 11th March 2020 (when the WHO declared COVID-19 pandemic).

A frequency table will be produced for the SAF analysis set to present the number of subjects with any of the above-listed study events attributable to COVID-19.

Additional COVID-19-related outputs will also be produced for protocol deviations, adverse events, and exposure. Please refer to those sections of this document for further details.

10.3 Reporting of Protocol Deviations

Analysis set: SAF

Please see Section 8.1 for details on the definition and collection of protocol deviations.

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

- Frequency table by reason of IPDs
- Frequency table of IPDs attributed to the impact of the COVID-19 pandemic
- Listing of IPDs

- Listing of protocol deviations attributed to the impact of COVID-19, including severity level of the deviation (important vs. non-important)

11 Demographics and Other Baseline Characteristics

11.1 Demographics

Analysis set: SAF

Demographic characteristics will be listed and summarized by dose level and overall as follows:

- Demographic characteristics
  - Gender: male, female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not collected at this site, other
  - Ethnicity: Hispanic or Latino, Not Hispanic or Latino
  - Age (years)
  - Age categories:
    - < 65 years, ≥ 65 years
    - 65-74, 75-84, ≥ 85
- Eastern Cooperative Oncology Group Performance Status (ECOG PS)
- Physical measurements
  - Height (cm)
  - Weight (kg)
  - BMI (kg/m^2)

Specifications for computation:

- Age [years]
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day for at least one date, but month and year available for both dates, the day of informed consent and the day of birth will be set to 1 and the formula above will be used.
  - In case of missing month for at least one date, but year available for both dates, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used.
- Site codes will be used for the determination of the participant's pooled region.

- BMI (kg/m²) = weight (kg) / [height (cm) x height (cm)] x 10000

A listing showing the relevant demographic data will also be produced.

11.2 Medical History

Analysis set: SAF

The medical history will be summarized from the "Medical History Details" eCRF pages, using the latest version of Medical Dictionary for Regulatory Activities (MedDRA), preferred term (PT) as event category and MedDRA system organ class (SOC) body term as body system category.

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

A supportive listing of medical history data by participant will include all the relevant data fields as collected on the "Medical History" eCRF page.

11.3 Other Baseline Characteristics

Disease Characteristics

Analysis set: SAF

Information regarding disease characteristics collected on the "Disease History" CRF page will be summarized and listed as follows:

- Type of cancer: Breast cancer, serous epithelial ovary cancer, bladder cancer, colon cancer, non-small cell lung cancer, castration resistant prostate cancer, stomach cancer, uterine cancer, melanoma, small cell lung cancer, rectal cancer, prostate cancer, other cancers
- Tumor histopathologic/ cytologic grade: GX: Grade cannot be assessed (undetermined grade), G1: Well differentiated (low grade), G2: Moderately differentiated (intermediate grade), G3: Poorly differentiated (high grade), G4: Undifferentiated (high grade)
- Time since initial cancer diagnosis (months), defined as (date of first study treatment – date of initial diagnosis)/30.4375
- Time since documented locally advanced, inoperable, or metastatic disease diagnosis (months), defined as (date of first study treatment – date of documented locally advanced, inoperable, or metastatic disease diagnosis)/30.4375
- Stage at initial diagnosis
- Stage at study entry
- TNM classification at initial diagnosis
- TNM classification at study entry

Site of primary tumor and subsites will be presented in a listing.

12 Previous or Concomitant Medications/Procedures

Analysis set: SAF

12.1 Prior Anti-Cancer Treatments

The prior anti-cancer treatments and procedures are collected from the "Prior Anti-cancer Surgeries Details", "Prior Anti-cancer Drug Therapies Details", and "Prior Anti-cancer Radiotherapy 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
- Type of prior anti-cancer drug therapy: Cytotoxic therapy / Endocrine therapy / Monoclonal antibody therapy / Small molecules / Immunotherapy / Other
- Intent of Therapy: Neoadjuvant / Adjuvant / Metastatic or Locally advanced
- For Metastatic/ Locally advanced intent, number of therapy lines: 1 / 2 / 3 / ≥4
- Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Non-CR/Non-PD / Progressive Disease (PD) / Not Evaluable (NE) / Unknown. Best response is derived from the last treatment regimen.

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

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

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

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

12.1 Previous and Concomitant Medications/Procedures

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

Previous medications are medications, other than study medications and pre-medications for study intervention, which are started before first administration of any study intervention.

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

Previous medications and concomitant medications will be summarized separately showing the number of subjects and percentage of subjects having taken a given drug, summarized by Anatomical Therapeutic Chemical classification class (ATC-2nd level) and PT, displayed by dose level and overall. ATC and PT will be summarized as given from the World Health Organization (WHO) dictionary current version. In case multiple ATCs are assigned to a drug, all ATC-2nd level will be used for reporting. In case the date values will not allow for unequivocal classification of a medication as concomitant, the medication will be considered as a concomitant medication.

A subject will be counted only once within a given drug class and within a given drug name, even if the subject received the same medication at different times or multiple medications within a given drug class.

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

Previous and concomitant medication data will be listed separately. The following variables will be included in the listings: cohort dose level, subject identifier, and all corresponding collected data fields on the corresponding eCRF pages. The listings will be sorted by cohort dose level, subject identifier, and the start date of the medication.

Prior and concomitant procedures data collected on the "Prior Anti-cancer Surgeries Details" and "Concomitant Procedures Details" eCRF pages will be listed. Cohort dose level, subject identifier, and all collected data fields on the corresponding eCRF pages will be included in the listings. The listings will be sorted by cohort dose level, subject identifier, and the start date of the procedure.

Premedication data (reported on the "Premedication Details" eCRF page) given before each study intervention administration will be listed.

12.2 Subsequent Anti-Cancer Therapies/Procedures

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

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 subsequent anti-cancer treatment
- Subjects with at least one subsequent anti-cancer drug therapy
- Subjects with at least one subsequent anti-cancer radiotherapy
- Subjects with at least one subsequent anti-cancer surgery
- Type of subsequent anti-cancer therapy: Cytotoxic therapy / Endocrine therapy / Monoclonal antibody therapy / Small molecules / Immunotherapy / Other
- Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Non-CR/Non-PD / Progressive Disease (PD) / Not Evaluable / Unknown. Best response is derived from the last treatment regimen.

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

13 Study intervention Compliance and Exposure

Analysis set: SAF

All dosing calculations and summaries, as well as the listings of study drug administration, will be based on the "M3814 Administration Details", "M3814 Accountability" "Avelumab Administration Details," "Radiotherapy Administration" "M3814 Termination", "Avelumab Termination" and "Radiotherapy Termination" eCRF pages.

- **Part A and Part FE**: M3814 will be administered twice daily, without interruption, in combination with avelumab, administered once every two weeks, starting on Day 1 until PD or unacceptable toxicity.

- **Part B**: M3814 will be administered once a day. RT will be given at the dose of 3 Gy per day. M3814 and RT will both be given starting Day 1 for 5 days/week for 2 weeks, at which point, both M3814 and RT are discontinued. Avelumab will be administered once every two weeks starting on Day 1 until PD or unacceptable toxicity.

Duration of therapy

Study intervention duration will be calculated based on the number of planned administration days expected for each treatment component. Duration of therapy is defined as follows:

Parts A and FE:

$$\text{Duration of avelumab (weeks)} = \left(\frac{\text{date of last dose} - \text{date of first dose} + 14}{7}\right)$$

$$\text{Duration of M3814 (weeks)} = \left(\frac{\text{date of last dose} - \text{date of first dose} + 1}{7}\right)$$

Part B:

$$\text{Duration of avelumab (weeks)} = \left(\frac{\text{date of last dose} - \text{date of first dose} + 14}{7}\right)$$

$$\text{Duration of M3814 (weeks)} = \left(\frac{\text{date of last dose} - \text{date of first dose} + 3}{7}\right)$$

$$\text{Duration of RT (weeks)} = \left(\frac{\text{date of last dose} - \text{date of first dose} + 3}{7}\right)$$

Duration of therapy will be summarized on a table with summary statistics for each treatment by cohort dose level. Details will also be included in a listing.

Cumulative dose

The overall cumulative dose per subject across all cycles is the sum of actual doses the subject received (i.e., total dose administered).

Cumulative dose is measured in mg for avelumab and M3814 and Gy for radiotherapy.

Cumulative actual dose will be summarized on a table with summary statistics for each treatment, by cohort dose level. Details will also be included in a listing.

Dose Intensity

Each cycle is defined by a 2-week period. M3814 will be administered once a day for 5 days followed by 2 days off for 10 days in total (i.e., on the same schedule as the RT). Avelumab will be administered Q2W as an IV infusion over 1 hour, starting on Day 1, at a fixed dose of 800 mg in all dose levels.

The dose intensity will be calculated for each subject across all cycles.

Dose intensity is defined for avelumab (mg/cycle), M3814 (mg/cycle), and RT (Gy/cycle) as follows:

$$\text{Dose Intensity} = \left(\frac{\text{actual cumulative dose}}{\frac{\text{duration of therapy (weeks)}}{\text{2 weeks/cycle}}}\right)$$

Dose intensity will be summarized on a table with summary statistics for each treatment, by cohort dose level. Details will also be included in a listing.

Relative Dose Intensity

The relative dose intensity is defined as the actual dose intensity divided by the per-protocol planned dose level per cycle and is expressed as a percentage.

$$\text{Relative Dose Intensity} = \left(\frac{\text{Dose Intensity}}{\text{planned dose level per cycle}}\right)$$

Relative dose intensity for each treatment will be included in a listing and will be summarized in the following categories, by cohort dose level:

- <50%
- 50% to < 80%
- 80% to < 90%
- 90% to 110%
- > 110%

Dose Reductions

For avelumab, a dose reduction is defined as an actual non-zero dose < 90% of the per-protocol dose within a given cycle.

For M3814, a dose reduction is defined as an actual non-zero cumulative dose < 90% of the planned (per-protocol) cumulative dose for a given treatment cycle (i.e., two-week period). Any skipped doses within the cycle will contribute to the calculation of the dose reduction (i.e., will be included in the denominator of the calculation). If a subject permanently discontinues treatment before completing a full cycle, the planned cumulative dose will be calculated as planned cumulative dose expected between the first dose of treatment on the cycle and the last.

Dose reductions are counted on a per-cycle basis and do not consider whether previous doses were reduced.

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

Therapy Delays

Therapy delays are only defined for avelumab administration and are defined as infusions given ≥3 days from the planned administration date. Delays are only defined for subjects who receive at least two administrations of avelumab and will be derived based on the time between two administrations:

$$\text{Therapy Delay} = [\text{date of current administration}] - [\text{date of previous administration}] - 14$$

Delays will be grouped into the following categories:

- No delay (including delay of 1-2 days)
- Delay of 3-6 days
- Delay of 7-13 days
- Delay of 14-20 days
- Delay of ≥21 days

The number and percentage of subjects with delayed avelumab administration and the longest observed delay (days) per subject will be summarized by cohort dose level. If possible, the number and percentage of subjects with therapy delays attributable to the COVID-19 pandemic will also be presented.

Therapy Interruptions

A therapy interruption is defined as omission of a full cycle of a planned study intervention. Therapy interruptions are only defined if the intervention is later restarted.

Avelumab: A therapy delay of greater than 13 days is considered a therapy interruption.

M3814 (Parts A and FE only): fourteen consecutive days of missed M3814 is considered a therapy interruption.

The number and percentage of subjects with an interruption in study drug administration and the longest observed interruption (cycles) per subject will be summarized by cohort dose level. If possible, the number and percentage of subjects with therapy interruptions attributable to the COVID-19 pandemic will also be presented.

14 Efficacy Analyses

14.1 Best Overall Response

Analysis sets: FAS

The confirmed Best Overall Response (BOR) is defined as the best confirmed response obtained among all tumor assessments after the start of study intervention until documented disease progression or start of subsequent anti-cancer treatment, taking requirements for confirmation into account as detailed below. Confirmed BOR will be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 based on the Investigator's assessment of disease.

Only tumor assessments performed on or 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. If a tumor assessment was performed on the same day as start of

new anti-cancer therapy, it will be assumed that the tumor assessment was performed prior to the start of the new anti-cancer therapy, therefore the tumor assessment will be included in the assessment of BOR.

Table 6 summarizes the derivation rules described by Eisenhauer, et al. for the BOR when confirmation from subsequent assessment is needed. For subjects who have non-target lesions only at baseline, the time-point tumor assessment of "Non-CR/non-PD" will be evaluated with the same criteria as SD (minimum criteria for SD duration) in deriving the overall BOR.

Table 6: Best Overall Response When Confirmation of CR/PR Is Required

Overall response 1st time point	Overall response subsequent time point	Best overall response (BOR)
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met; otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met; otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

BOR based on confirmed responses:

- CR = at least two determinations of CR at least 4 weeks apart (with no PD in between)
- 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), with no PD in between
- SD (applicable only to participant with measurable disease at baseline) = at least one SD assessment (or better) ≥ 8 weeks after start date (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to participants with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 8 weeks after start date (and not qualifying for CR or PR).

- PD = PD ≤ 16 weeks after start date (and not qualifying for CR, PR, non-CR/non-PD or SD).
- Not Evaluable (NE): all other cases.

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

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

The number and percentage of subjects with BOR of CR, PR, SD, PD, non-CR/non-PD (applicable only to subjects with non-measurable disease at baseline), and NE will be tabulated. Subjects with BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No Baseline Assessment
- No post-baseline assessments due to death within 8 weeks after treatment start
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after treatment start without further evaluable tumor assessment)
- PD too late (i.e., tumor assessment of PD was >16 weeks after treatment start and there was no tumor assessment in between)

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

Objective Response

The confirmed objective response rate (ORR) is defined as the proportion of subjects having reached a confirmed BOR of CR or PR according to RECIST v1.1, as evaluated by the Investigator. Subjects with BOR of non-CR/non-PD are not considered to have achieved objective response. Subjects who do not have a post-baseline radiographic tumor assessment due to early progression; who receive anti-cancer treatments other than the study intervention 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 ORR.

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

14.2 Duration of Response

Analysis sets: FAS

Duration of Response (DOR) is defined only for subjects with an OR. DOR is calculated as the time from first documentation of OR (CR or PR according to RECIST 1.1, as evaluated by the Investigator) to the date of first documentation of objective progression of disease or death due to any cause. For subjects with an OR but neither documented disease progression nor death as of the cut-off date for the analysis, DOR will be censored at the date of the last adequate tumor assessment. The censoring rules for DOR are the same as those described for progression-free survival (PFS) in Section 14.4.

DOR (months) = (date of PD or death – date of 1st objective response + 1)/30.4375

Kaplan-Meier (i.e., product-limit) estimates of median DOR time will be presented by cohort dose level together with two-sided 95% CIs calculated according to Brookmeyer and Crowley (3). The number of subjects at risk (i.e., with ongoing response) vs. failed along with Kaplan-Meier estimates of ongoing response probability at 3, 6, and 12 months will be estimated with corresponding two-sided 95% CIs derived using the log-log transformation according to Kalbfleisch and Prentice (4) (i.e., CONFTYPE=loglog default option in SAS LIFETEST procedure). The estimate of the standard error will be computed using Greenwood's formula.

If the number of subjects with OR is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

14.3 Tumor Shrinkage

Analysis sets: FAS

Tumor shrinkage is defined only for subjects with both a baseline and post-baseline tumor assessment and is derived as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesions and short axis for nodal lesions) at each time point. See Section 9.1 for the definition of baseline and percent change from baseline.

The percent change from baseline in target lesions as well as the first occurrence of a new lesion and subject off treatment will be displayed against time point (weeks) in a line/spider plot. The lines of the plot will be color coded according to cohort dose level.

The maximum percent reduction in target lesions from baseline will be identified across all the post-baseline assessments until documented PD or start of subsequent anti-cancer treatment. The maximum percent reduction is equivalent to the smallest percent change from baseline.

A waterfall plot of the maximum percent reduction in target lesions from baseline will also be created. Bars in the waterfall plot will be color coded according to cohort dose level.

For Part B, a listing with details of the irradiated lesions will be provided.

14.4 Progression Free Survival

Analysis sets: FAS

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

PFS time (months) = (Date of event or censoring – Treatment start date + 1)/ 30.4375

If a tumor assessment was performed on the same day as start of new anti-cancer therapy, it will be assumed that the tumor assessment was performed prior to the start of the new anti-cancer therapy; therefore, the tumor assessment will be included in the derivation of the PFS time.

An adequate tumor assessment is defined as a result that is not "NE" or "NA" (Not Applicable).

The censoring and event date options for the PFS and DOR analyses are presented in Table 7.

Table 7: Outcome and Event Dates for PFS and DOR Analyses

Scenario	Date of event / censoring	Outcome
No adequate baseline assessment	Treatment day 1	Censored [a]
If the last tumor assessment is beyond 6 months from the first dose: Progression or death ≤ 24 weeks after last tumor assessment	Date of progression or death	Event
If the last tumor assessment is within 6 months from the first dose: Progression or death ≤ 16 weeks after last tumor assessment or ≤ 16 weeks after treatment day 1	Date of progression or death	Event
If the last tumor assessment is beyond 6 months from the first dose: Progression or death > 24 weeks after last tumor assessment	Date of last evaluable assessment	Censored
If the last tumor assessment is within 6 months from the first dose: Progression or death > 16 weeks after last tumor assessment	Date of last evaluable assessment	Censored
No progression	Date of last evaluable assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable.	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last evaluable tumor assessment before anti-cancer therapy is given	Censored

[a] However if the subject dies ≤ 16 weeks after treatment day 1, the death is considered an event with date on death date.

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

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

Frequency (number and percentage) of subjects with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 8 following the hierarchy shown.

Table 8: PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy before event	Start of new anti-cancer therapy
3	Event more than 16 (or 24 if beyond 6 months from the first dose of study treatment) weeks after last adequate post-baseline tumor assessment / date of first dose of study treatment (see also Table 7)	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 eCRF page	Lost to follow-up
6	No event and EOS present 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 16 (or 24) weeks after last adequate tumor assessment (see also Table 7)

14.5 Overall Survival

Overall Survival (OS) is defined as the time from treatment start to the date of death, regardless of the actual cause of the subject's death. For subjects who are still alive at the time of the data cut-off for the analysis or who are lost to follow up, OS time will be censored at the last recorded date that the subject is known to be alive as specified in Section 9.4.

OS (in months) = (Date of death – Date of first study treatment administration +1) / 30.4375

Kaplan-Meier (i.e., product-limit) estimates of median OS time will be presented by cohort dose level together with two-sided 95% CIs calculated according to Brookmeyer and Crowley (1). The number of subjects at risk vs. failed along with Kaplan-Meier estimates of survival probability at 3, 6, and 12 months (as well as further timepoints as appropriate) will be estimated with corresponding two-sided 95% CIs derived using the log-log transformation according to Kalbfleisch and Prentice (2) (i.e., CONFTYPE=loglog default option in SAS LIFETEST procedure). The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of subjects with an event (death) and censoring reasons will also be presented by treatment arm. Censoring reasons are as follows:

- Ongoing in the study without an event
- Withdrawal of consent
- Lost to follow-up

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

15 Safety Analyses

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

15.1 Adverse Events

Analysis set: SAF

The severity of AEs will be graded using the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5. If a particular AE's severity is not specifically graded by this guidance, the Investigator uses the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment. The latest MedDRA version at the time of data cut-off will be used to code AEs according to SOC and PT.

- **Treatment Emergent Adverse Events** (TEAEs) are events with onset dates occurring during the on-treatment period, or those that worsen in severity during the on-treatment period. All analyses will be based on TEAEs unless otherwise specified.
- **Related Adverse Events** have a relationship to study treatment of "Related", or missing relatedness, as reported by the Investigator on the "Adverse Events Details" eCRF page. Relatedness is defined separately for each study intervention component.
- **Serious Adverse Events** (SAEs) are those recorded on the "Adverse Events Details" eCRF page as Serious Adverse Event = "Yes".
- **Adverse Events Leading to Treatment Discontinuation** are those recorded on the "Adverse Events Details" eCRF page as Action(s) taken with M3814/ avelumab/ radiotherapy = "Drug withdrawn".
- **Adverse Events Leading to Death** are those recorded on the "Adverse Events Details" eCRF page as Outcome = "Fatal" as well as AEs of Grade 5.
- **Adverse Events of Special Interest** (AESIs) for this study include infusion related reactions (IRRs) / hypersensitivities and immune-related AEs (irAEs) / autoimmune disorders. IRRs and irAEs are identified based on a list of MedDRA PTs and other qualifying criteria, as specified in Appendix I.

Details on the handling of incomplete AE-related dates are specified in Section 9.4.

15.1.1 All Adverse Events

Adverse events will be summarized by worst severity per subject, using MedDRA PT as event category and SOC as summary category, in alphabetical order. If an AE is reported for a given subject more than once during treatment, the worst severity and the worst relationship to study treatment will be tabulated.

An overall summary table of AEs will be prepared and will tabulate the number and percentage of participants with AEs in the following categories:

- Any TEAE
- TEAEs related to study intervention (tabulated by relatedness to any study intervention, and individual study intervention components)
- Any serious TEAEs
- Serious TEAEs related to study intervention (tabulated by relatedness to any study intervention, and individual study intervention components)
- TEAEs with NCI-CTCAE severity Grade ≥ 3
- TEAEs related to study intervention with NCI-CTCAE severity Grade ≥ 3 (tabulated by relatedness to any study intervention, and individual study intervention components)
- TEAEs leading to death
- TEAEs related to study intervention leading to death (tabulated by relatedness to any study intervention, and individual study intervention components)
- Treatment-emergent AESIs overall and by category (see Section 15.2.4 for more details on summaries of AESIs)

In addition, tables summarizing the frequency of subjects with AEs, presented by SOC and PT, in the following categories will be prepared. Tables summarizing TEAEs related to study intervention will be created to summarize TEAEs related to any study intervention and will be repeated to summarize TEAEs related to specific study intervention components (M3814, avelumab, and, for Part B, RT).

- Any TEAE
- TEAEs by worst grade
- TEAEs related to study intervention
- Serious TEAEs
- Serious TEAEs related to study intervention
- TEAEs related to study intervention by worst grade
- TEAEs leading to death
- TEAEs related to study intervention leading to death

Clinical trial.gov and EudraCT requirements

Summary tables for nonserious AEs, applying frequency threshold of 5% in any dose level when excluding SAEs, by SOC and PT, will be provided.

Details of the AESIs will be presented in a listing sorted by SOC and PT, including: Subject number, SOC, PT, AESI category, relationship to avelumab, seriousness, grade, start date, cohort dose level, and time since last and first administration of avelumab.

A listing of all AEs will also be prepared, including all relevant details from the "Adverse Events Details" eCRF page. A flag will be included in the listing, identifying AEs attributed to COVID-19.

15.1.2 Adverse Events Leading to Study Intervention Discontinuation

An overall summary table of AEs leading to permanent study intervention discontinuation will be prepared and will tabulate the number and percentage of participants with AEs in the following categories:

- Any TEAE leading to permanent discontinuation of at least one study intervention
- TEAEs leading to permanent discontinuation of M3814
- TEAEs leading to permanent discontinuation of avelumab
- TEAEs leading to permanent discontinuation of RT (Part B only)
- TEAEs leading to permanent discontinuation of both M3814 and avelumab
- TEAEs related to M3814 leading to its permanent discontinuation
- TEAEs related to avelumab leading to its permanent discontinuation
- TEAE related to both leading to permanent discontinuation
- TEAEs related to RT leading to its permanent discontinuation
- AESIs leading to permanent discontinuation of avelumab, by category

In addition, tables summarizing the frequency of subjects with TEAEs, presented by SOC and PT, in the following categories will be prepared.

- TEAEs leading permanent discontinuation of avelumab
- TEAEs leading permanent discontinuation of M3814
- TEAEs leading permanent discontinuation of RT (Part B only)
- TEAEs leading permanent discontinuation of M3814 and avelumab
- TEAEs related to avelumab leading to its permanent discontinuation
- TEAEs related to M3814 leading to its permanent discontinuation

As action taken with study intervention will be detailed in the full listing of AEs, no separate listing of AEs leading to permanent discontinuation of study intervention will be produced.

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

15.2.1 Occurrence of DLTs

Analysis set: DLT

The occurrence of DLTs during the DLT evaluation period is a primary endpoint for both Parts A and B of the study. The DLT period for Part A is defined as the first 3 weeks of the study, following the start of the study intervention. The DLT period for Part B is defined as the first 4 weeks of the study, following the start of study intervention. The DLT Analysis Set will be used for the analysis of the primary endpoint. Please refer to Section 6.6.3 of the Clinical Trial Protocol MS201964-0001 for the detailed definition of a DLT. Determination of whether an AE is considered a DLT is made by the Investigator and specified on the "Adverse Events Details" eCRF page; this assessment is subsequently confirmed by the SMC.

A summary table of DLTs will include the following summaries:

- Number and percentage of subjects who experienced a DLT during the DLT evaluation period
- Number and percentage of subjects experiencing any AE during the DLT evaluation period.
- Number of DLTs experienced per subject: 1 /2 /≥3
- DLTs by SOC and PT

A listing of DLTs will include subject identifier, dose level, and all relevant variables from the "Adverse Events Details" eCRF page.

In addition, a DLT profile plot of all subjects in the Safety Analysis Set will be produced. This will show a closed square for all subjects who were considered evaluable (i.e. included in DLT Analysis Set) and did not have a DLT during the DLT period, an open square for those who experienced a DLT during the DLT period, and an open circle for those who were excluded from the DLT Analysis Set. This plot will have cohort number on the x-axis and dose level (mg) on the y-axis.

15.2.2 Deaths

Analysis set: SAF

All deaths after first study intervention will be tabulated based on information from the "Death" eCRF page. The summary will be displayed by cohort dose level and will include:

- Number of deaths overall and by primary reason
- Number of deaths within 30 days after last dose of study intervention
- Number of deaths within 60 days after first dose of study intervention

In addition, date and cause of death will be provided in an individual participant data listing together with selected dosing information, presented separately for each intervention (date of first / last administration, dose, number of cycles/ fraction days, and relatedness to each study intervention). The listing will include columns for:

- AEs with fatal outcome
- Flag for death within 30 days of last study intervention
- Flag for death within 60 days of first study intervention
- Flag for death related to COVID-19

15.2.3 Serious Adverse Events

Analysis set: SAF

Please refer to Section 15.1.1 for details on SAE summaries.

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

15.2.4 Adverse Events of Special Interest

Analysis set: SAF

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

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

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

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

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

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

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

15.3 Clinical Laboratory Evaluation

Analysis set: SAF

15.3.1 Hematology and Clinical Chemistry Parameters

All statistical analyses of laboratory values will be performed using SI units.

Any subject with an abnormal hematology or chemistry result will have all records for the parameter with the abnormal result included in a listing. Pertinent details, including value, change from baseline, normal range indicator, and toxicity grade (where applicable) will be provided.

Quantitative data will be examined for trends in actual values and the change from baseline through presentation of boxplots shown over time, at each visit. In addition, a boxplot of the change from baseline to the worst on-treatment record for each parameter will be produced.

Listings will include all the hematology and chemistry laboratory parameters as available in the database with the all corresponding relevant information.

Parameters with CTCAE grade defined

Please see Appendix II – NCI-CTC Gradable and Non-Gradable Safety Laboratory Test Parameters and Direction(s) of Abnormalityfor a list of the CTCAE-gradable parameters.

Laboratory toxicities will be tabulated (count and percentage) for each gradable parameter by the worst on-treatment CTCAE grade. Shifts from baseline to worst CTCAE grade during the on-treatment period will also be tabulated. For some parameters (indicated in Appendix II), the on-treatment grading is dependent upon the baseline grading; in such cases, the baseline grading

(normal vs. abnormal) will be displayed together with the on-treatment grading in the tabular summaries.

The denominator to calculate percentages for each laboratory parameter is the number of patients in the cohort dose level. Subjects without baseline or post-baseline results for a given parameter will be presented in the "Missing" category and will contribute to the denominator.

Parameters with no CTCAE grade defined

Laboratory abnormalities will be tabulated (count and percentage) for each non-gradable parameter by the worst on-treatment abnormality. Shifts from baseline to worst abnormality (separately for high and low criteria) during the on-treatment period will also be tabulated. The denominator to calculate percentages for each laboratory parameter is the number of patients in the cohort dose level. Subjects without baseline or post-baseline results for a given parameter will be presented in the "Missing" category and will contribute to the denominator.

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

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

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

- ALT $\geq$ 3×ULN, ALT $\geq$ 5×ULN, ALT $\geq$ 10×ULN, ALT $\geq$ 20×ULN
- AST $\geq$ 3×ULN, AST $\geq$ 5xULN, AST $\geq$ 10×ULN, AST $\geq$ 20×ULN
- (ALT or AST) $\geq$ 3×ULN, (ALT or AST) $\geq$ 5×ULN, (ALT or AST) $\geq$ 10×ULN, (ALT or AST) $\geq$ 20×ULN
- Total Bilirubin $\geq$ 2×ULN
- Concurrent ALT $\geq$ 3×ULN and TBILI $\geq$ 2×ULN
- Concurrent AST $\geq$ 3×ULN and TBILI $\geq$ 2×ULN
- Concurrent (ALT or AST) $\geq$ 3×ULN and TBILI $\geq$ 2×ULN
- Concurrent (ALT or AST) $\geq$ 3×ULN and TBILI $\geq$ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) $\geq$ 3×ULN and TBILI $\geq$ 2×ULN and ALP $\leq$ 2×ULN or missing

Concurrent measurements are those occurring on the same date.

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

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created by graphically displaying peak serum ALT (/ULN) vs peak Total Bilirubin (/ULN) including

reference lines at ALT ≥3xULN and bilirubin ≥2xULN. The display will be divided into 4 quadrants by the lines through ALT ≥ 3×ULN and Total Bilirubin ≥2×ULN. The left lower quadrant is then considered normal or insignificant elevations in liver chemistries, the left upper quadrant indicates patients with possible Gilbert's cholestasis; the right upper quadrant are the possible Hy's Law patients; the right lower quadrant is possible Temple's Corollary (patients with ALT ≥ 3 x ULN but not satisfying Hy's Law). Different symbol will be used for different cohort dose levels.

15.3.2 Other laboratory parameters

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

- Urinalysis: all urinalysis parameters
- Hormones: free thyroxine (T4) and thyroid-stimulating hormone (TSH)
- Serology: HIV and hepatitis
- Pregnancy test

15.4 Vital Signs

Analysis set: SAF

The maximum changes of vital sign measurements from baseline to maximum change during the on-treatment period will be grouped as follows:

Table 9: Vital Signs Summary Categories

Vital Sign Baseline Category	Change from Baseline Category
Body temperature increase	< 1°C, 1-<2°C, 2-<3°C, ≥ 3 °C
Heart rate increase from baseline <100 bpm; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
Heart rate decrease from baseline <100 bpm; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
SBP increase from baseline <140 mmHg; ≥ 140 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
SBP decrease from baseline <140 mmHg; ≥ 140 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP increase from baseline <90 mmHg; ≥ 90 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP decrease from baseline <90 mmHg; ≥ 90 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
Respiration rate increase from baseline <20 bpm; ≥ 20 bpm	≤5 bpm, >5 – 10 bpm, >10 bpm
Respiration rate decrease from baseline <20 bpm; ≥ 20 bpm	≤5 bpm, >5 – 10 bpm, >10 bpm

The following summaries will be prepared for vital sign parameters as grouped above considering only participants with post-baseline values:

- Maximal shifts (changes in categories)
- Listing of highest change per participant

An additional participant data listing will present all pertinent vital signs details collected throughout the course of the study.

15.5 Other Safety or Tolerability Evaluations

Analysis set: SAF

15.5.1 12-Lead Electrocardiogram

The incidence and percentage of subjects with potentially clinically significant abnormalities (PCSA) for 12-lead ECG parameters will be summarized during the on-treatment period. The PCSA criteria are provided in the Table 10.

Table 10: Potentially Clinically Significant Abnormalities Criteria for ECG

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

(a) $QTcF$ (Fridericia's Correction) = $QT/\sqrt[3]{RR}$ (RR-interval is measured in seconds) will be summarized as collected in eCRF.

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

15.5.2 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status (ECOG PS) will be summarized using a shift table showing baseline versus worst post-treatment value. The information will come from the "ECOG Performance Status" eCRF page.

Listings of each participant's ECOG PS over time will be provided.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

Population: PK analysis set

Non-compartmental computation of M3814 and *0*-demethylated product M467 (if available) PK parameters will be performed using the computer program Phoenix® WinNonlin® Version 8.0, or higher (Pharsight Corporation, a Certara Company, Princeton, New Jersey). The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary North Carolina), Version 9.2, or higher, will be used to produce tables, listings, and figures. Figures will be prepared with SAS Version 9.2, or higher.

Avelumab tables, listings, figures, and parameters will be computed using SAS.

Pharmacokinetic parameters will be calculated using standard non-compartmental methods, the actual administered dose, and actual elapsed time from dosing.

Pharmacokinetic concentrations of M3814 would be pooled with data from other studies to conduct a population PK analysis. A non-linear mixed effect approach would be used to characterize the blood concentration time profile of M3814 following multiple doses and to evaluate the PK inter-individual variability and the covariates that are predicting this variability. Provided sufficient amount of data, the FE will also be tested as a covariate in the model. Such analysis will be specified in a separate Pharmacometry analysis plan. Results will be presented separately from the main CSR.

Blood will be collected for M3814 (and *0*-demethylated product M467) and avelumab determination according to the following schedules:

Table 11: Pharmacokinetic Sampling Times for Part A and Part FE

Week (Day)	Time (h)	M3814 (Part A)	M3814 (Part FE)	Avelumab (both parts)
Week 1 (Day 1) and Week 3 (Day 15)	Predose	X	X	X
	1	X	X	
	EoI			X (Day 1 only)
	2	X	X	
	3	X	X (Day 15 only)	
	4	X	X	
	6	X	X	
Week 4 (Day 22)	Predose	X	X	
	2	X	X	
	4		X	
	6	X	X	
Week 5 (Day 29)	Predose	X		X
	EoI			X (Part A only)
Week 9 (Day 57)	Predose			X (Part A only)
Week 13 (Day 85)	Predose			X
Weeks 25, 37, 49	Predose			X
EoT*		X	X	X (Part A only)
30-Day Safety FU (if prior to Week 49)				X

For both Part A and Part FE, M314 will be administered twice daily, without interruption, in combination with avelumab (1 hour infusion), administered once every two weeks, starting on Day 1 until PD or unacceptable toxicity. In Part FE, subjects will be fed a high fat meal on Day 1 and Day 22 and will be fasted on Day 15.
EoI = end of infusion; EoT = end of treatment; FU = follow-up
* For M3814, only applies if M3814 treatment is stopped. For avelumab if prior to Week 49.

Table 12: Pharmacokinetic Sampling Times for Part B

Week (Day)	Time (h)	M3814	Avelumab
Week 1 (Day 1; FD1)	Predose	X	X
	1	X	
	EoI		X
	2	X	
	4	X	
	6	X	
Week 1 (Day 2; FD2)	Predose	X	
	2	X	
Week 2 (Day 8; FD6)	Predose	X	
	2	X	
Week 2 (Day 12; FD10)	Predose	X	
	2	X	
	4	X	
	6	X	
Week 3 (Day 15)	Predose		X
Week 5 (Day 29)	Predose		X
	EoI		X
Week 9 (Day 57)	Predose		X
Week 13 (Day 85)	Predose		X
Weeks 25, 37, 49	Predose		X
EoT*		X	X
30-day Safety FU			X

M3814 will be administered once a day. RT will be given at the dose of 3 Gy per day. M3814 and RT will both be given starting Day 1 for 5 days/week for 2 weeks, at which point both M3814 and RT are discontinued. Avelumab (1 hour infusion) will be administered once every two weeks, starting on Day 1 until PD or unacceptable toxicity.
EoI = end of infusion; EoT = end of treatment; FD = fraction day; FU = follow-up.
* For avelumab, if prior to Week 49.

Table 13: Acceptable Pharmacokinetic Window for Avelumab

Sampling Time	Time From Scheduled Sampling Allowed
Before BoI	Within 120 minutes prior to dose
EoI	Within 15 minutes before EoI

BoI = beginning of infusion; EoI = end of infusion

Table 14: Acceptable Pharmacokinetic Window for M3814

Sampling Time	Time From Scheduled Sampling Allowed
Predose	Within 60 minutes prior to dose administration
0.5 to 2 hours postdose	± 20 minutes
> 2 hours postdose	± 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.

PK concentrations which are erroneous due to a protocol violation (as defined in the CSP), sampling processing or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed by the Sponsor. In this case the rationale for exclusion must be provided in the Clinical Study Report (CSR). Any other PK concentrations that appear implausible to the Clinical Pharmacologist/Clinical PK/PD Scientist will not be excluded from the analysis. Any implausible data will be documented in the Clinical Study Report (CSR).

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

The following PK parameters will be reported for M3814 and *0*-demethylated product M467 (if available) on Day 1 (D1), Day 15 (D15), and Day 22 (D22) and in Part A and Part FE where data permit. Appropriate adjustments will be made for differences in molecular weight (MW) (M3814 MW = 481.92 $gmol^{-1}$; *0*-demethylated product M467 MW = 467.12 $gmol^{-1}$). Concentration results collected on Day 22, Day 29 (Part A), and EoT will be summarized descriptively.

C_{max} Maximum observed concentration.

C_{max}/Dose The dose-normalized maximum observed concentration (Part A only). Normalized using the actual dose, and the formula C_{max} /Dose.

C_{trough} The concentration observed immediately before next dosing on D15, D22, and D29, (D29 is Part A only).

C_{trough}/Dose The dose-normalized trough concentration. Normalized using the actual dose, and the formula C_{trough} /Dose on D15, D22, and D29, (D29 is Part A only).

AUC_{0-6} Area under the concentration-time curve (AUC) from time zero to time 6 hours postdose. AUC_{0-6} will be based on the estimated concentration at 6 hours and not the concentration at the actual observation time.

AUC_{0-6}/Dose The dose-normalized AUC from time zero to 6 hours postdose (Part A only). Normalized using the actual dose, using the formula AUC_{0-6}/Dose.

AUC_{0-12} AUC from time zero to time 12 hours postdose. $AUC_{0-12,D1}$ will be based on the estimated concentration at 12 hours after dosing. $AUC_{0-12,D15}$ from zero to 12 hours postdose with predose D15 concentration used for estimated concentration at 12 hours (Part A only).

AUC_{0-12}/Dose The dose-normalized AUC_{0-12} (Part A only). Normalized using the actual dose, using the formula AUC_{0-12}/Dose.

t_{max} Time to reach the maximum observed concentration C_{max}.

$R_{acc(Cmax)}$ Accumulation ratio for C_{max}, calculated as $C_{max,D15}/C_{max,D1}$ (Part A only).

$F_{rel(Cmax)}$ Relative bioavailability of C_{max} of fed (D22) compared to fasted (D15) $C_{max,fed}/C_{max,fasted}$ and C_{max} of fed (D1) compared to fasted (D15) $C_{max,fed}/C_{max,fasted}$ (Part FE only).

$R_{acc(AUC0-12)}$ Accumulation ratio for AUC_{0-12} calculated as $AUC_{0-12,D15}/AUC_{0-12,D1}$ (Part A only).

$F_{rel(AUC0-6)}$ Relative bioavailability for AUC_{0-6} of fed (D22) compared to fasted (D15) $AUC_{0-6,fed}/AUC_{0-6,fasted}$ and as sensitivity analysis AUC_{0-6} of fed (D1) compared to fasted (D15) $AUC_{0-6,fed}/AUC_{0-6,fasted}$ (Part FE only).

λ_z Terminal first order elimination rate constant.

$t_{½}$ Apparent terminal half-life, $t_{½} = \ln 2/\lambda_z$.

CCI [redacted]

[redacted]

The following PK parameters will be reported for M3814 on Day 1 (FD1) and Day 12 (FD10) in Part B where data permit. Concentration results collected on Day 2 (FD2), Day 8 (FD6), and EoT will be summarized descriptively.

C_{max} Maximum observed concentration

C_{max}/Dose The dose-normalized maximum observed concentration. Normalized using the actual dose, and the formula C_{max} /Dose.

C_{trough} The concentration observed immediately before next dosing on FD10 only.

C_{trough}/Dose The dose-normalized trough concentration. Normalized using the actual dose, and the formula C_{trough} /Dose on FD10 only.

AUC_{0-6} Area under the concentration-time curve (AUC) from time zero to time 6 hours postdose. AUC_{0-6} will be based on the estimated concentration at 6 hours and not the concentration at the actual observation time.

AUC_{0-6}/Dose The dose-normalized AUC from time zero to 6 hours postdose. Normalized using the actual dose, using the formula AUC_{0-6}/Dose.

AUC_{0-24} Area under the concentration-time curve (AUC) from time zero to time 24 hours postdose. $AUC_{0-24,FD1}$ will be based on the estimated concentration at 24 hours after dosing and not the concentration at the actual observation time. $AUC_{0-24,FD10}$ from zero to 24 hours postdose with predose FD10 concentration used for estimated concentration at 24 hours.

AUC_{0-24}/Dose The dose-normalized AUC from time zero to 24 hours postdose for FD1 and FD10. Normalized using the actual dose, using the formula $AUC_{0-24,FD1}$/Dose and $AUC_{0-24,FD10}$/Dose.

t_{max} Time to reach the maximum observed concentration C_{max}

$R_{acc(Cmax)}$ Accumulation ratio for C_{max}, calculated as $C_{max,FD10}/C_{max,FD1}$

$R_{acc(AUC0-6)}$ Accumulation ratio for AUC_{0-6} calculated as $AUC_{0-6,FD10}/AUC_{0-6,FD1}$

$R_{acc(AUC0-24)}$ Accumulation ratio for AUC_{0-24} calculated as $AUC_{0-24,FD10}/AUC_{0-24,FD1}$

$t_{½}$ Apparent terminal half-life, $t_{½} = \ln 2/\lambda_z$

CCI [redacted]

The following PK parameters will be reported for avelumab where data permit.

C_{EOI} Concentration observed at the end of infusion period.

C_{trough} Concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing).

$R_{acc(Ceoi)}$ Accumulation ratio for C_{EOI}, calculated as $C_{EOI,D29}/C_{EOI,D1}$ (Part A and Part B).

$R_{acc(Ctrough)}$ Accumulation ratio for C_{trough}, calculated as $C_{trough,D57}/C_{trough,D15}$ (Part A and Part B)

The following PK parameters will be calculated for M3814 or M467 for diagnostic purposes and listed, but will not be summarized:

- λ_z Terminal first order elimination rate constant
- First ($\lambda_{z\,low}$) and last ($\lambda_{z\,up}$) time point of the time of the log-linear regression to determine λ_z.
- Number of data points included in the log-linear regression analysis to determine λ_z.
- Goodness of fit statistic (Rsq,adj) for calculation of λ_z.

The calculation of the AUC will be performed using the mixed linear-log trapezoidal method. The actual time of blood sampling (14 significant digits or the SAS format Best12) will be used for PK parameter calculation. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time.

Values below the lower limit of quantification of the assay (LLOQ) will be taken as zero for summary statistics of PK concentration data, PK parameter estimation, and for graphical presentations. In case BLQ concentrations occur at the end of the dosing interval (24 h), these will be excluded from the calculation of the AUC_{0-24}.

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. Phoenix

WinNonlin "best fit" methodology will be used as standard. However, in some cases, further adjustment may be made by the pharmacokineticist, if warranted, after agreement with the Sponsor. The last quantifiable concentration should always be included in the regression analysis, while the concentration at t_{max} and any concentrations <LLOQ which occur after the last quantifiable data point should not be used.

The coefficient of correlation (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 constant and $t_{1/2}$ will be included in the parameter outputs and descriptive statistics but will be flagged and discussed appropriately. Any flags will be included in the study specific SDTM and ADaM data sets.

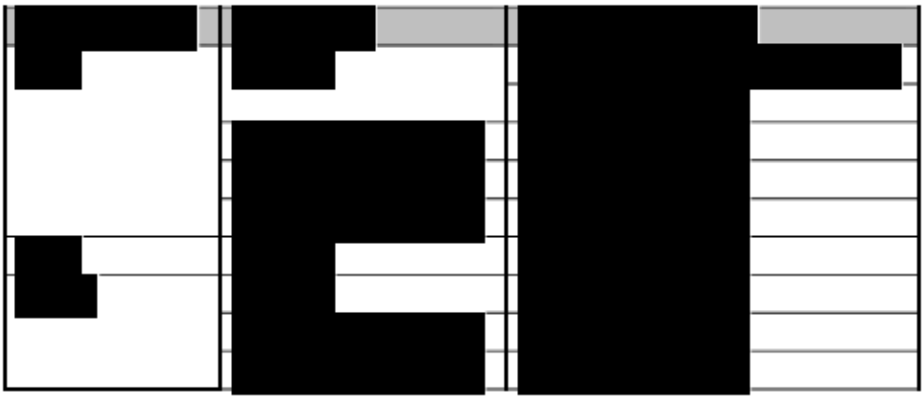
The following listings and summary statistics of M3814, *0*-demethylated product M467, and avelumab PK concentration and M3814 and *0*-demethylated product M467 parameter data will be provided:

- Listing of individual PK concentration data by analyte, part, dose, and scheduled time point
- Listing of individual single dose PK parameters by analyte, part, dose, and day
- Listing of individual multiple dose PK parameters by analyte, part, dose, and day
- Descriptive summary table of PK concentration data by analyte, part, dose, day, and scheduled time point
- Individual concentration-time profiles (linear and semi-logarithmic scales) will be plotted by analyte, dose level and day as spaghetti plots, using actual time points (where available). Separate profiles for fed and fasted treatments, Part FE.
- Additional spaghetti plots will be produced (on both linear and semi-log scale) to show the concentration-time data per dose level over the entire-time course. Separate profiles for fed and fasted treatments, Part FE.
- Arithmetic mean concentrations will be plotted on both linear (±StDev) and semi-logarithmic scales using scheduled time points – with all dose levels overlaid per day, and with all days overlaid per dose level. Additional mean plots will be produced (on both linear (±StDev) and semi-log scale) to show the mean concentration-time data per dose level over the entire-time course. Additional individual profiles and mean plots for fed and fasted treatments: overlay plots D1/D15 and D15/D22 for Part FE.
- Scatter plots of dose-normalized C_{max}, dose-normalized AUC_{0-6}, and dose-normalized AUC_{0-12} or dose-normalized AUC_{0-24} (as applicable) against dose (all days).
- Paired data plots of C_{max} and AUC_{0-6} against fed and fasted, Day 22 and Day 15, Day 1 and Day 15 respectively, for Part FE.

All descriptive summaries of PK data will be performed using the PK Analysis Set. Individual PK data will be listed using the Safety Analysis Set. The mean concentration-time profiles and PK parameter plots will be plotted using the PK Analysis Set and the individual subject concentration-time profiles will use the Safety Analysis Set.

CCI [redacted]

CCI [redacted]



CCI [redacted]

16.3 Immunogenicity

Blood samples for anti-drug antibody (ADA) analysis will be collected per the Schedule of Assessments in the Clinical Trial Protocol and tested for presence of anti-avelumab ADA. All samples will be screened for the detection of ADA and those detected will be subsequently evaluated for a confirmatory signal. If the sample is confirmed positive for ADA, it will be re-analyzed to determine the titer. Independently for each assay, the ADA results will be derived based on the algorithm in Table 16.

Subjects will be characterized by immunogenicity status based on the criteria in Table 17.

Table 16: Algorithm for the Derivation of ADA Results

Sample Screen Result	Confirmatory	Titer	Derived ADA Result
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 17: Subject Characterization Based on ADA Results

Category	Definition	Subject at Risk (Denominator for Incidence)
Never positive	No positive results at any time point	Number of subjects with at least one valid result at any time point
Ever positive	At least one positive result at any time point	Number of subjects with at least one valid result at any time point
Pre-existing	A positive ADA result prior to treatment with avelumab	Number of subjects with valid baseline result
Treatment boosted	A positive ADA result prior to treatment with avelumab and the titer $\geq$ 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 $\geq$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)

NR: Not reported;

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

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

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

17 References

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-47.
2. Clopper, C. J., & Pearson, E. S. (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika, 26, 404–413.
3. Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. Biometrics 1982;38:29-41.
4. 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 Definition for Assessment of irAEs and IRRs

Immune-Related Adverse Events

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

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

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

3) On the AE eCRF page, the question "Is this an adverse event of special interest?" has the response "imAEs / autoimmune disorders" selected.

IRRs

Infusion related reactions are identified based on a list of MedDRA PTs and criteria on the timely relationship according to Table 18Table 18.

Table 18: Criteria for infusion related reactions

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

Appendix II – NCI-CTC Gradable and Non-Gradable Safety Laboratory Test Parameters and Direction(s) of Abnormality

Table 19: NCI-CTC gradable parameters

Category	Parameter	Name in NCI-CTC	Direction(s) of abnormality
Serum chemistry			
Electrolytes	Calcium	Hypocalcemia/Hypercalcemia	Low/High
Electrolytes	Magnesium	Hypomagnesemia/Hypermagnesemia	Low/High
Electrolytes	Potassium	Hypokalemia/Hyperkalemia	Low/High
Electrolytes	Sodium	Hyponatremia/Hypernatremia	Low/High
Enzymes/cardinal	Creatinine Phosphokinase	CPK increased	High
Enzymes/cardinal	Lactate dehydrogenase	Blood lactate dehydrogenase increased	High
Enzymes/liver	Alanine Aminotransferase	Alanine Aminotransferase increased *	High
Enzymes/liver	Alkaline Phosphatase	Alkaline Phosphatase increased *	High
Enzymes/liver	Aspartate Aminotransferase	Aspartate Aminotransferase increased *	High
Enzymes/liver	Gamma-glutamyl transferase	GGT increased *	High
Enzymes/liver	Total bilirubin	Blood bilirubin increased *	High
Metabolism	Glucose	Hypoglycemia	Low
Metabolism	Urate (uric acid)	Hyperuricemia	High
Plasma proteins	Albumin	Hypoalbuminemia	Low
Renal/kidney	Creatinine	Creatinine increased *	High
Hematology			
Platelets	Platelets Count	Platelet count decreased	Low
Red blood cells	Hemoglobin	Anemia/Hemoglobin increased	Low/High
White blood cells/differential	White Blood Cell Count	White blood cell decreased/Leukocytosis	Low/High
White blood cells/differential	Absolute Lymphocytes Count	Lymphocyte count decreased/increased	Low/High
White blood cells/differential	Absolute Neutrophils Count	Neutrophil count decreased	Low
White blood cells/differential	Eosinophils	Eosinophilia *	High

* indicates parameters for which the on-treatment grading depends upon the baseline grading.

Table 20: NCI-CTC non-gradable parameters

Category	Parameter (LBTEST)	Direction(s) of abnormality
Serum chemistry		
Electrolytes	Phosphate	Low
Metabolism	Glucose	High
Plasma proteins	Total protein	Low
Renal/kidney	Blood Urea Nitrogen	High
Hematology		
Red blood cells	Hematocrit	High/Low
Red blood cells	Mean Corpuscular Hemoglobin	High/Low
Red blood cells	Mean Corpuscular Hemoglobin Concentration	High/Low
Red blood cells	Mean Corpuscular Volume	High/Low
Red blood cells	Red blood cells (Erythrocytes)	High/Low
Red blood cells	Reticulocytes	High/Low
White blood cells/differential	Basophils	High
White blood cells/differential	Monocytes	High/Low