Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS201944-0170
Title	A Phase IIa, single-arm, multicenter study to investigate the clinical activity and safety of avelumab in combination with cetuximab plus gemcitabine and cisplatin in participants with advanced squamous non-small-cell lung cancer (NSCLC)
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Integrated Analysis Plan Reviewers	**Function** — **Name** PPD, PPD — PPD Global Biostatistics Lead, Merck Healthcare KGaA — PPD Global Biostatistics Lead, Merck Healthcare KGaA — PPD PPD, Merck Healthcare KGaA — PPD PPD, Merck Healthcare KGaA — PPD PPD, Merck Healthcare KGaA — PPD PPD, Merck Healthcare KGaA — PPD Principal Clinical Trial Lead, EMD Serono — PPD PPD, Merck Healthcare KGaA — PPD PPD, Merck Healthcare KGaA — PPD PPD, Merck Healthcare KGaA — PPD PPD, Merck Healthcare KGaA — PPD PPD, Merck Healthcare KGaA — PPD PPD, EMD Serono — PPD PPD, EMD Serono — PPD Stat Programming Lead, Merck Healthcare KGaA — PPD PPD, Merck Healthcare KGaA — PPD PPD, Merck Healthcare KGaA — PPD

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Approval Page

Integrated Analysis Plan: MS201944-0170

A Phase IIa, single-arm, multicenter study to investigate the clinical activity and safety of avelumab in combination with cetuximab plus gemcitabine and cisplatin in participants with advanced squamous non-small-cell lung cancer (NSCLC)

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

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2 List of Abbreviations and Definition of Terms

ADA	Antidrug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BOR	Best Overall Response
BSA	Body Surface Area
C_{eoi}	Immediate End of Infusion Observed Concentration
CI	Confidence Interval
C_{max}	Maximum Observed Concentration
COVID-19	2019 Novel Coronavirus Disease
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE v5.0	Common Terminology Criteria for Adverse Events Version 5.0
C_{trough}	The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing)
DOR	Duration of Response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
ENR	Enrolled Analysis Set/Population
CCI	[redacted]
EoT	End of Treatment
FAS	Full Analysis Set/Population
FDA	Food and Drug Administration
GBS	Global Biostatistics
HR	Hazard Ratio
IAP	Integrated Analysis Plan
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
irAE	Immune-related Adverse Event
IRC	Independent Review Committee
iv	Intravenous
KM	Kaplan-Meier

LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minumum
N	Number of subjects
n	Number of subjects with non-missing values
NA	Not Applicable
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not Evaluable
Non-CR/Non-PR	Non-Complete Response/Non-Progressive Disease
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PCSA	Potentially Clinically Significant Abnormalities
CCI [redacted]	
PD	Progressive Disease
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Death Ligand 1
PFS	Progression Free Survival
CCI [redacted]	
CCI [redacted]	
PK	Pharmacokinetics
PKAS	Pharmacokinetics Analysis Set
PR	Partial Response
CCI [redacted]	
PT	Preferred Term
CCI [redacted]	
RECIST v1.1	Response evaluation criteria in solid tumors version 1.1
SAE	Serious Adverse Event
SAF	Safety Analysis Set/Population
CCI [redacted]	
SCR	Screening analysis population
SD	Stable Disease
SMC	Safety Monitoring Committee
SOC	System Organ Class
StdDev	Standard Deviation

TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
CCI [redacted]	
TNM	Tumor Node Metastasis
TPS	Tumor Proportion Score
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	21Jan2020	PPD	Initial Version
2.0	10Aug2020	PPD	1. Added note about for COVID-19 related important protocol deviations in Section 8.1. 2. Added imputation rules for partial dates of subsequent anti-cancer therapy. 3. Specified that the reasons for treatment and study discontinuation in the disposition table will include COVID-19 as options. 4. Added table and listing of important protocol deviations related to COVID-19 in Section 10.2.1. 5. Corrected cumulative dose and dose intensity of carboplatin to be in units of mg instead of mg/m^2 in Section 13. 6. Updated therapy delay derivation in Section 13 to follow the protocol-specified schedule instead of being calculated relative to the previous administration. 7. Added sensitivity analyses of Confirmed BOR and PFS for population subsets related to COVID-19; specified that sensitivity analyses will only be conducted if <95% of the FAS would be included. 8. Added Time to Response as a change to the planned analyses. 9. CCI [redacted] 10. Added listing of AEs related to COVID-19. 11. Updated algorithm for identifying irAEs in Section 15.1 and added derivation details to Appendix I. 12. Added COVID-19 as a possible cause of death to be summarized. 13. Updated eDISH plot description in Section 15.3.1 to use peak instead of concurrent total bilirubin. CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] 18. Added Section 16.4 to describe analyses of COVID-19 impact. 19. Updated NCI-CTC laboratory gradable/non-gradable parameters in Appendix II to reflect what was actually collected on this study. 20. Updated list of abbreviations; removed all references to analyses “by treatment group” that came from the IAP template; other minor editorial revisions.

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for both the Main Analysis and the Final Analysis of data collected for Protocol MS201944-0170. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon section 9 (Statistical Considerations) of the study protocol and any potential protocol amendments and is prepared in compliance with ICH E9. It describes analyses planned in the protocol and protocol amendments. Details of the Safety Monitoring Committee (SMC) analyses for review of the participants' safety without formal statistical analysis are provided in appendices.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
To evaluate efficacy by means of confirmed best overall response (BOR) rate of the combination of cetuximab and avelumab plus doublet chemotherapy, defined as the proportion of participants having achieved confirmed complete response (CR) or partial response (PR) as BOR	Confirmed BOR according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) assessed by Investigator	14.1.1
Secondary		
To evaluate the safety and tolerability of the combination of cetuximab and avelumab plus doublet chemotherapy	Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AEs), treatment-related Grade ≥ 3 AEs, and immune-related AEs, according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0)	15.1, 15.2
To evaluate the progression-free survival (PFS) time	PFS time according to RECIST v1.1 by Investigator assessment	14.2.1
To assess the duration of response (DOR)	DOR assessed from confirmed CR or PR until progression of disease (PD), death, or last tumor assessment according to RECIST v1.1	14.2.1
To assess overall survival (OS)	OS	14.2.1
To characterize pharmacokinetic (PK) profiles of avelumab and cetuximab when given in combination with chemotherapy	Peak and trough avelumab and cetuximab serum concentration at pre-specified study visits	16.1
CCI [redacted]		

6 Overview of Planned Analyses

Safety Monitoring Committee (SMC) meetings will be performed at the end of the safety run-in, as well as at other subsequent, pre-specified timepoints. The specific working procedures are described in the SMC Charter. Although no interim analyses are planned, unplanned analyses may be conducted for the purpose of data review and regulatory updates.

To further evaluate preliminary antitumor activity of the combination regimen, assessment by an independent review committee (IRC) might be conducted retrospectively in case of promising results that warrant further exploration of this treatment. If conducted, this IAP will be amended to cover the analysis details.

6.1 Main Analysis

The Main Analysis is planned at 5 months after last patient first visit. Although no interim analyses prior to the Main Analysis are planned, unplanned analyses may be performed.

6.2 Final Analysis

The Final Analysis will be conducted when data collection is completed, 12 months after the last participant receives the last dose.

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

7 Changes to the Planned Analyses in the Clinical Study

The following objectives noted in the Clinical Trial Protocol will be investigated for possible further analysis following a positive study outcome, which is defined as 18 or more responders (confirmed CR or PR) out of 40 treated participants. These analyses will be included in an addendum to this main IAP, or a separate IAP as appropriate.

Objectives	Endpoints (Outcome Measures)
Secondary	
To characterize the immunogenicity of the combination therapy with cetuximab and avelumab and chemotherapy	Immunogenicity of cetuximab and of avelumab in combination therapy, as measured by separate antidrug antibody (ADA) assays
CCI [redacted]	

CCI

[redacted]

Additionally, in the derivation of BOR, the required timeframe for determination of PD was changed to ≤ 18 weeks (as opposed to ≤ 12 weeks, as specified in the Protocol). This update was made due to the planned interval of tumor assessments, which are scheduled to occur every 9 weeks for the first 6 months of treatment.

One further efficacy endpoint, time to response (TTR) was determined to be of interest despite not being pre-specified in the Protocol. The analysis of TTR consists of simple summary statistics (mean, SD, median, min, max, Q1, Q3) based on participants in the FAS with confirmed objective response. The value is calculated as:

TTR (weeks) = (Date of first CR or PR – Date of first dose +1)/7

Finally, the COVID-19 pandemic was unforeseen at the time this Protocol was finalized; therefore, the respective sensitivity analyses were added later.

8 Protocol Deviations and Analysis Populations

8.1 Definition of Protocol Deviations and Analysis Populations

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

Important protocol deviations include:

- Participants that are dosed on the study despite not satisfying the inclusion criteria
- Participants that develop withdrawal criteria whilst on the study but are not withdrawn
- Participants that receive the wrong study intervention or an incorrect dose
- Participants that receive an excluded concomitant medication
- Deviation from Good Clinical Practice

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

Separate summaries will be provided for all protocol deviations and the subset of protocol deviations that were attributed to the impact of the COVID-19 pandemic.

8.2 Definition of Analysis Populations and Subgroups

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock.

Enrolled Analysis Set (ENR)

The enrolled analysis set includes all participants who signed the informed consent form.

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

The full or safety analysis set will include all participants who receive at least one non-zero dose of any study treatment.

Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic (PK) analysis set will consist of all participants who receive at least one dose of avelumab and/or cetuximab, have no important events affecting PK, and provide at least one measurable post-dose concentration.

Subgroup definition and parameterization:

Subgroup analyses will be performed on primary and secondary efficacy endpoints based on the subgroups of the SAF Analysis Set, as defined below.

CCI [redacted] The purpose of subgroups sex, age, and country are to check internal consistency within the targeted population. Subgroups histology, Eastern Cooperative Oncology Group Performance Status (ECOG PS) and smoking habits are known prognostic for lung cancer patients. In the case of a low number of participants within a category (<10% of the population), the categories will be pooled when meaningful.

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Diagnostic status 80: ≥80% of tumor cells with intensity 2+ or 3+ (Diagnostic status 80 positive)

Diagnostic status 80: <80% of tumor cells with intensity 2+ or 3+ (Diagnostic status 80 negative)

Diagnostic status 90: ≥90% of tumor cells with intensity 2+ or 3+ (Diagnostic status 90 positive)

Diagnostic status 90: <90% of tumor cells with intensity 2+ or 3+ (Diagnostic status 90 negative)

CCI [redacted]

- Sex (male versus female)
- Age (< 65 versus ≥ 65 years)
- Country (Spain versus Hungary versus Serbia)
- ECOG performance status at baseline (0 versus 1)
- Smoking history (ever smoker versus never-smoker)
- Liver metastases at baseline (yes versus no)
- Brain metastases at baseline (yes versus no)
- Previously treated for non-metastatic disease (yes versus no)

9 General Specifications for Data Analyses

Unless otherwise indicated, summary tables will be presented based on the analysis set of interest; listings will be presented using the same analysis sets as corresponding tables.

There is no formal significance level for this study and all analyses are considered descriptive.

Pooling of centers:

Data will be pooled across centers.

Presentation of continuous and qualitative variables:

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

- number of subjects (N); number of subjects with non-missing values (n)
- arithmetic mean (Mean), standard deviation (StdDev)
- median, 25th Percentile - 75th Percentile (Q1-Q3)
- minimum (Min), maximum (Max)
- 95% confidence intervals (CIs) for the mean, as appropriate

Qualitative variables will be summarized by counts and percentages.

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

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

Definition of baseline:

The last non-missing measurement prior to the first administration of any study treatment will serve as the baseline measurement.

Definition of duration:

Duration will be calculated by the (difference of start and stop date) + 1 (e.g., survival time (days) = date of death – date of treatment start + 1) (if not otherwise specified).

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

Unscheduled visits:

Assessments from unscheduled visits will be used for the derivation of baseline values and worst on-treatment values. However, descriptive statistics by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits per protocol.

Conversion factors:

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

Handling of missing data:

Unless otherwise specified, missing data will not be replaced.

In all subject 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 (StdDev) cannot be computed and will be presented as "nd".

Treatment day

Treatment day is defined relative to the start date of study treatment. Treatment Day 1 is the day of the first administration of any study treatment. The day before Treatment Day 1 is defined as Treatment Day -1. (No Treatment Day 0 is defined.)

Date of last contact

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

- All participant assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments, quality of life assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation.
- AE start and end dates
- Last known to be alive date collected on the 'Subject Status / Survival Follow-up' eCRF
- Study drug start and end dates
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

Only dates associated with actual examinations of the participant reported in the eCRF will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

Handling of incomplete dates:

Disease history

Incomplete dates for disease history (initial diagnosis date, date of confirmed stage IV (metastatic or recurrent) diagnosis) will be imputed as follows:

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

Adverse events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2019, and study treatment start date is 15/JAN/2019, then the imputed AE onset date will be 15/JAN2019.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2019, and study treatment start date is 19/NOV/2019, then the imputed AE onset date will be 19/NOV/2019.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after date of cut-off outcome of AE is ongoing at cut-off.

Further information after cut-off (like fatal outcome) might be taken from the Safety database and included separately into the CSR.

Prior/concomitant medication

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

- If the medication start date is missing completely, then the medication date will be replaced by the start of study treatment.
- If the day of medication start date is missing, but the month and year are equal to the start of study treatment, then the medication start date will be replaced by the start of study treatment. For example, if the medication start date is --/JAN/2019, and study treatment start date is 15/JAN/2019, then the imputed medication start date will be 15/JAN2019.
- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2019, and study treatment start date is 19/NOV/2019, then the imputed medication start date will be 19/NOV/2019.
- In all other cases the missing medication day or missing medication month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date.

- In all other cases the incomplete medication stop date will not be imputed.

Subsequent anti-cancer therapy

Incomplete dates for start date of subsequent anti-cancer therapy (drug therapy, radiation, and 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.
- Incomplete subsequent anti-cancer therapy stop dates will not be imputed.

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

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

On-treatment period

The on-treatment period is defined as the date of the first dose of initial study treatment until the minimum (last dose date + 30 days, earliest date of subsequent anti-cancer drug therapy – 1 day).

Definiton of Missing category

If not otherwise specified the following categories will be summarized under the missing category:

- missing
- unknown

SAS version:

All analyses will be performed using PPD version 9.4 or higher.

Presentation of PK Concentration and PK Parameter Data

The presentation of PK concentration and PK parameter data is described in detail in Section 16.1 Pharmacokinetics. There will be no imputation of missing data. Concentrations will be set to missing in summary tables if the value is reported as no result.

10 Study Participants

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

10.1 Disposition of Participants and Discontinuations

Analysis set: ENR

The disposition table will include the following information:

- Number of participants screened
- Number and percentage of participants who discontinued from the study prior to treatment, overall and by reason for discontinuation
- Number of participants in the FAS/SAF analysis set
- Number and percentage of participants who took at least one dose of gemcitabine
- Number and percentage of participants who took at least one dose of cisplatin
- Number and percentage of participants who took at least one dose of carboplatin
- Number and percentage of participants who took at least one dose of avelumab
- Number and percentage of participants who took at least one dose of cetuximab
- Number and percentage of participants still on treatment
- Number and percentage of participants off-treatment
- Number and percentage of participants who discontinued the treatment but are still in follow-up
- Number and percentage of participants who completed the chemotherapy period
- Number and percentage of participants who discontinued gemcitabine, overall and by reason for discontinuation
- Number and percentage of participants who discontinued cisplatin, overall and by reason for discontinuation
- Number and percentage of participants who discontinued carboplatin, overall and by reason for discontinuation
- Number and percentage of participants who discontinued avelumab, overall and by reason for discontinuation
- Number and percentage of participants who discontinued cetuximab, overall and by reason for discontinuation
- Number and percentage of participants who re-initiated avelumab treatment

- Number and percentage participants who re-initiated avelumab treatment and discontinued the treatment after re-initiation, overall and by reason of discontinuation
- Number and percentage of participants who discontinued assessment, overall and by reason for discontinuation
- Number and percentage of participants who discontinued the study, overall and by discontinuation reason

A summary of participants who discontinued one or more treatments and/or the study for reasons attributed to the COVID-19 pandemic will be provided.

Separate summary tables of analysis populations as well as enrollment for each country and site will be provided.

All relevant disposition data will be presented in data listings including reasons for exclusion from analysis sets.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

Analysis set: SAF

The following summary tables and listings of important protocol deviations will be provided (separately for pre-/post inclusion deviations):

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

The above table and listing will be repeated, including only the subset of important deviations that are attributed to the impact of COVID-19, as reported in CTMS.

10.2.2 Reasons Leading to the Exclusion from an Analysis Population

For participants excluded from the PK, the reasons for exclusion will be listed and summarized using frequency counts:

- Did not receive avelumab or cetuximab
- Important events affecting PK
- No measureable post-dose concentration

11 Demographics and Other Baseline Characteristics

Analysis set: FAS

11.1 Demographics

Demographic characteristics will be summarized using the following information from the Screening/Baseline Visit CRF pages.

The following demographic characteristics will be included:

- Sex: male, female
- Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, not collected, other
- Age (years): summary statistics
- Age categories:
  - < 65 years, ≥ 65 years
- Country:
  - Hungary
  - Serbia
  - Spain
- Height (cm) at Baseline: summary statistics
- Weight (kg) at Baseline: summary statistics
- Body Surface Area (BSA) at Baseline: summary statistics
- Body Mass Index (BMI) at Baseline: summary statistics
- Eastern Cooperative Oncology Group (ECOG) Performance Status: 0 or 1

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:

  For the derivation of age, 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:

  For the derivation of age, 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

- BMI (kg/m^2) = weight (kg) / [height (cm) x height (cm)] x 10000

All relevant demographic data will be presented in data listings.

Baseline characteristics with respect to vital signs, physical examinations, and hematology/biochemistry will be part of Section 15 (Safety Evaluation).

11.2 Medical History

Analysis set: FAS

The medical history will be summarized from the "Medical History" eCRF page, 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 subject will include all the relevant data fields as collected on the "Medical History" eCRF page.

11.3 Other Baseline Characteristics

Analysis set: FAS

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

- Site of primary tumor
- Disease stage at initial diagnosis including Tumor Node Metastasis Classification of Malignant Tumors (TNM) status
- Time since initial diagnosis (months) defined as (start date of first study drug – date of initial cancer diagnosis)/30.4375
- Histopathological classification: Squamous histology, Other
- Disease stage at study entry including TNM status
- Liver metastases at baseline
- Brain metastases at baseline

Gene mutations will be extracted from the "Disease History" eCRF page and summarized as follows:

- Kirsten rat sarcoma viral oncogene homolog (KRAS) (mutated / not mutated / unknown)
- Proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B (BRAF) (mutated / not mutated / unknown)
- (ROS1) (mutated / not mutated / unknown)
- Anaplastic Lymphoma Kinase (ALK) (mutated / not mutated / unknown)

A listing of disease history as collected on the "Disease History" eCRF page will be provided with all relevant data (primary tumor site, initial diagnosis date, date of confirmed stage IV, histopathological classification, stage (at initial diagnosis and study entry), TNM classification at initial diagnosis and study entry, and gene mutations) and derived variables used in the above table.

Nicotine consumption will be summarized as follows:

- Nicotine use status (never used / regular user / occasional user / former user)
- Exposure type (cigarettes / cigars / pipes / chewing tobacco / nicotine gum / e-cigarettes and vapor)
- Exposure summary statistics per week for each exposure type

A listing of nicotine consumption as collected on the "Nicotine Consumption" eCRF page will be provided with all relevant data.

11.4 Prior Anti-cancer Treatments and Procedures

Analysis set: SAF

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

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

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

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of participants with the following:

- At least one prior anti-cancer drug therapy
- Any prior anti-cancer therapy regimens: missing / 1 / 2 / 3 / $\geq$4
- Type of therapy: cytotoxic therapy, monoclonal antibodies therapy, targeted therapy, or other
- Intent of prior anti-cancer drug therapy: neoadjuvant, adjuvant, locally advanced, or other
- Best response to regimen from prior anti-cancer drug therapy: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), non-complete response/non-progressive disease (Non-CR/Non-PD), not evaluable (NE), or unknown

- Time elapsed since most recent anti-cancer drug therapy to first study treatment (months) defined as (start date of first study drug – end date of latest prior anti-cancer drug therapy +1 day)/30.4375: summary statistics

- Duration of most recent anti-cancer drug therapy (months) defined as (end date of latest prior anti-cancer drug therapy – start date of latest prior anti-cancer drug therapy + 1 day)/ 30.4375: summary statistics

Summary of prior radiotherapy will be summarized according to the eCRF page "Prior Anti-Cancer Radiotherapy Details".

- Number of participants with at least one prior radiotherapy

- Best response to regimen from prior anti-cancer radiotherapy: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), non-complete response/non-progressive disease (Non-CR/Non-PD), not evaluable (NE), or unknown

The following listings of prior anti-cancer therapies will also be provided:

- Listings of prior anti-cancer drug therapies

- Listing of prior radiotherapies

- Listing of prior anti-cancer surgeries as collected on the "Prior Anti-Cancer Surgeries Details" eCRF page.

These will include subject identifier and all the relevant data collected on the corresponding eCRF pages. Drugs given as part of the prior anti-cancer drug therapies will be included in the respective listing. Anatomical Therapeutic Chemical (ATC)-2nd level and preferred term will be tabulated as given from the latest version of World Health Organization-Drug Dictionary (WHO-DD). In case multiple ATCs are assigned to a drug, all ATC-2nd level will be used for reporting.

12 Concomitant Medications/Procedures

Analysis set: SAF

12.1 Previous Medications

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

The only previous medications collected per eCRF are those captured as part of the "Prior Anti-Cancer Drug Therapies" and will be listed as noted in Section 11.4.

12.2 Concomitant Medications

Concomitant medications are medications, other than study medications, which are taken by participants during the on-treatment period (on or after the first day of study intervention for each

participant or min(within 30 days after last dose of study treatment, earliest date of subsequent anti-cancer drug therapy – 1 day)).

Concomitant treatment will be summarized from the "Concomitant Medications Details" eCRF page. ATC-2nd level and preferred term will be tabulated as given from the WHO-DD 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 unequivocal allocation of a medication as a concomitant medication, the medication will be considered a concomitant medication.

All relevant concomitant medication data will be listed.

12.3 Concurrent Procedures

All **concurrent procedures**, which are taken by participants during the on-treatment period (on or after the first day of study intervention for each participant or min (within 30 days after last dose of study treatment, earliest date of subsequent anti-cancer drug therapy – 1 day)), will be summarized according to the eCRF page "Concomitant Procedures Details".

Concurrent procedures will be derived in the same way as concomitant medications. In case the date values will not allow unequivocal allocation of a procedure as a concurrent procedure, the procedure will be considered a concurrent procedure.

All concurrent procedure data will be listed, including flags for procedures that took place prior to, on or after the date of first study intervention, or within 30 days after the last dose of a study treatment.

12.4 Anti-Cancer Post-Intervention

Anti-cancer therapy after end of study intervention that will be summarized according to the CRF page "Anti-Cancer Treatment After Discontinuation Details". In addition, concomitant medication will be checked for post-interventions by medical review. Treatments will be categorized by means of coding and medical review.

- Number of participants with at least one anti-cancer treatment after discontinuation
- Type of therapy: cytotoxic therapy, monoclonal antibodies therapy, targeted therapy, or other
- Intent of therapy: neoadjuvant, adjuvant, locally advanced, or other
- Best response across all regimens from anti-cancer treatment after discontinuation: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), non-complete response/non-progressive disease (Non-CR/Non-PD), not evaluable (NE), or unknown

All relevant anti-cancer treatment after discontinuation data will be listed 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

Dosing information is collected from the "Avelumab Administration Details", "Cetuximab Administration Details", "Cisplatin Administration Details", "Carboplatin Administration Details" , "Gemcitabine Administration Details", and "Premedication Details" eCRF pages.

- Gemcitabine and cisplatin will be administered in 3-week cycles up to a maximum of 4 cycles of intravenous (iv) infusions until disease progression or unacceptable toxicities. Gemcitabine (1250 mg/m^2) is administered on Day 1 and Day 8 and cisplatin (75 mg/m^2) is administered on Day 1 of each 3-week cycle.
    - At the discretion of the Investigator, a switch to carboplatin for the remainder of the platinum-doublet cycles (up to 4 cycles in total) will be allowed in participants developing unacceptable toxicities to cisplatin. In these participants, carboplatin will be administered on Day 1 of each 3-week cycle at a dose of target area under the serum concentration-time curve of 5 (AUC 5) using the Calvert formula:

      Dose (mg) = (5 mg/mL*min) x [GFR (mL/min) + 25 (mL/min)]
- Avelumab (800 mg iv) will be administered on Day 1 and Day 8 of each 3-week cycle for the first 4 cycles along with concurrent chemotherapy as per schedule. Thereafter, avelumab will be given every 2 weeks in the Maintenance phase until disease progression or unacceptable toxicities.
- Cetuximab will be administered during the first 4 cycles of concurrent chemotherapy, with an iv dose of 250 mg/m^2 body surface area on Day 1 of each cycle and at a dose of 500 mg/m^2 body surface area on Day 8 of each cycle. Thereafter, cetuximab will be given every 2 weeks in the Maintenance phase, at the dose of 500 mg/m^2 iv until disease progression or unacceptable toxicities.

Total number of infusions

For each of the study medications, the total number of infusions is calculated as the sum of the actual number of infusions that a participant received for that medication across cycles, regardless of infusion delays, interruptions, or any other deviations from the protocol required schedules. An infusion is regarded to be administered if either the actual dose received is > 0 mg or the duration of the infusion is > 0 minutes.

Duration of therapy

Duration of therapy (in weeks) during the study will be calculated differently based on the dosing days and frequency as follows:

Gemcitabine, Avelumab, and Cetuximab: During each 21-day cycle, gemcitabine, avelumab, and cetuximab are administered by iv infusion on treatment Days 1 and 8. Duration of therapy during the chemotherapy treatment period is calculated as follows:

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

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

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

where the *addon* is 14 when the last dose is given on day 8 of the last cycle and *addon* is 7 when the last dose is given on day 1 of the last cycle.

Cisplatin or Carboplatin: During each 21 day cycle, cisplatin or carboplatin is administered by intravenous infusion on Day 1 of the cycle (excluding Cycle 1 for Carboplatin). Duration is calculated as follows:

Duration of Cisplatin (weeks) = $\left(\frac{date\ of\ last\ dose - date\ of\ first\ dose + 21}{7}\right)$

Duration of Carboplatin (weeks) = $\left(\frac{date\ of\ last\ dose - date\ of\ first\ dose + 21}{7}\right)$

Duration of Cisplatin plus Carboplatin (weeks) = Duration of Cisplatin (weeks) + Duration of Carboplatin (weeks)

Participants will be considered as having received a maintenance therapy when the chemotherapy (gemcitabine and cisplatin or carboplatin) has been definitely stopped (after four cycles) and at least one dose of cetuximab and/or avelumab has been received after the date of last chemotherapy dose.

The duration of maintenance therapy (in weeks) for participants with avelumab and cetuximab maintenance is defined as:

$$\text{duration} = \left(\frac{date\ of\ last\ dose\ drug\ maintenance - date\ of\ first\ dose\ drug\ maintenance + 14}{7}\right)$$

where the date of first dose of maintenance therapy is the date of first dose of respective drug after the date of last dose in the final chemotherapy cycle.

Overall duration of therapy for avelumab and cetuximab is the sum of the duration during the chemotherapy and maintanence treatment periods.

Cumulative dose

Gemcitabine, cisplatin, and cetuximab: The cumulative dose (mg/m²) per participant in a time period is the sum of the total dose levels that the participant received within that period (i.e., total dose administered (mg) / BSA (m^2)). For study drugs administered based on the participant's BSA, the calculation will be based on the BSA measured at each relavant visit. In case the BSA is missing, the latest BSA available will be used for calculation following the last observation carried forward (LOCF) principle. The individual dose administered (mg) is taken from the "Actual Dose"

field from the respective "Administration Details" eCRF pages at each dosing day. Each individual actual dose is then divided by the relavant BSA and summed across the time period of interest.

Avelumab and carboplatin: The cumulative dose (mg) per participant in a time period is the sum of the total dose levels that the participant received within that period. The individual actual dose (mg) is taken from the "Actual Dose" field from the respective "Administration Details" eCRF page at each dosing day.

Dose intensity

- Gemcitabine

$$\text{Dose intensity (mg/m}^2\text{/3-week cycle)} = \left(\frac{\textit{Cumulative dose of Gemcitabine } (mg/m^2)}{(\textit{duration of Gemcitabine (in weeks)}/3)}\right)$$

- Cisplatin

$$\text{Dose intensity (mg/m}^2\text{/3-week cycle)} = \left(\frac{\textit{Cumulative dose of Cisplatin } (mg/m^2)}{(\textit{duration of Cisplatin (in weeks)}/3)}\right)$$

- Carboplatin

$$\text{Dose intensity (mg/3-week cycle)} = \left(\frac{\textit{Cumulative dose of Carboplatin } (mg)}{(\textit{duration of Carboplatin (in weeks)}/3)}\right)$$

- Cetuximab during the chemotherapy period

$$\text{Dose intensity (mg/m}^2\text{/3-week cycle)} = \left(\frac{\textit{Cumulative dose of Cetuximab } \left(\frac{mg}{m^2}\right)}{(\textit{duration of Cetuximab (in weeks)}/3)}\right)$$

- Cetuximab during maintenance period

$$\text{Dose intensity (mg/m}^2\text{/2-week cycle)} = \left(\frac{\textit{Cumulative dose of Cetuximab } (mg/m^2)}{(\textit{duration of Cetuximab (in weeks)}/2)}\right)$$

- Avelumab during the chemotherapy period

$$\text{Dose intensity (mg/3-week cycle)} = \left(\frac{\textit{Total Cumulative dose of Avelumab } (mg)}{(\textit{duration of Avelumab (in weeks)}/3)}\right)$$

- Avelumab during maintanence period

$$\text{Dose intensity (mg/2-week cycle)} = \left(\frac{\textit{Total Cumulative dose of Avelumab } (mg)}{(\textit{duration of Avelumab (in weeks)}/2)}\right)$$

Relative dose intensity

The relative dose intensity of avelumab is defined as the actual dose intensity divided by the planned dose as specified in the protocol per cycle and expressed in %:

- Gemcitabine

$$\text{Relative intensity (\%)} = \left(\frac{\textit{Actual dose intensity Gemcitabine } (mg/m^2/cycle)}{2500\ mg/m^2}\right)$$

- Cisplatin

$$\text{Relative intensity (\%)} = \left(\frac{\textit{Actual dose intensity Cisplatin } (mg/m^2/cycle)}{75\ mg/m^2}\right)$$

- Carboplatin

$$\text{Relative intensity (\%)} = \left(\frac{\textit{Actual dose intensity Carboplatin } (AUC)}{AUC\ 5}\right)$$

- Cetuximab during the chemotherapy period

$$\text{Relative intensity (\%)} = \left(\frac{\textit{Actual dose intensity Cetuximab } (mg/m^2/cycle)}{750\ mg/m^2}\right)$$

- Cetuximab during the maintenance period

$$\text{Relative intensity (\%)} = \left(\frac{\textit{Actual dose intensity Cetuximab } (mg/m^2/cycle)}{500\ mg/m^2}\right)$$

- Avelumab during the chemotherapy period

$$\text{Relative intensity (\%)} = \left(\frac{\textit{Actual dose intensity Avelumab } (mg/cycle)}{1600\ mg}\right)$$

- Avelumab during the maintenance period

$$\text{Relative intensity (\%)} = \left(\frac{\textit{Actual dose intensity Avelumab } (mg/cycle)}{800\ mg}\right)$$

The following summary tables will be provided:

For the chemotherapy treatment period

- Number of cycles
- Total number of infusions received overall and by cycle for each study drug
- Duration of therapy (weeks) for each study drug
- Cumulative dose (mg for avelumab and carboplatin; mg/m^2 for gemcitabine, cisplatin, and cetuximab)
- Dose intensity (mg/3-week cycle for avelumab and carboplatin; mg/m^2/3-week cycle for gemcitabine, cisplatin, and cetuximab)
- Relative dose intensity of therapy (%) for each study drug

- Relative dose intensity of therapy categories: < 80%, 80% - < 90%, 90% - < 110%, >= 110%.

For the maintenance treatment period

- Number and percentage of participants with maintenance for each study drug
- Number of maintenance cycles for participants with maintenance for each study drug
- Duration of therapy (weeks) for each study drug
- Overall duration of therapy (weeks) for each study drug
- Cumulative dose (mg for avelumab and mg/m^2 for cetuximab)
- Dose intensity (mg/2-week cycle for avelumab and mg/m^2/2-week cycle for cetuximab)
- Relative dose intensity of therapy (%) for each study drug

Dose reductions

Dose reductions are identified by the Investigator on the "Administration Details" eCRF pages for Gemcitabine, Cetuximab, Cisplatin, and Carboplatin. The number and percentage of participants with at least one dose reduction as recorded in the eCRF, as well as a breakdown of dose reductions (1 / 2 / 3 / ≥4), will be summarized for each study drug.

Infusion rate reductions

For each study drug, infusion rate reductions are identified on the "Administration Details" eCRF page by the Investigator. The number and percentage of participants with at least one infusion rate reduction as recorded in the eCRF, as well as a breakdown of infusion rate reductions (1 / 2 / 3 / ≥4), will be summarized for each study drug.

Therapy Delays

Therapy delays will be derived for each study drug by infusion based on study drug administration date. Delays will be grouped into the following categories based on the deviation to the planned treatment administration day (according to the protocol-specified schedule):

- No delay (including 1-2 day delays)
- 3-8 day delay
- 9-15 day delay
- >= 16 day delay

All relevant study drug exposure data will be presented in data listings, including dose reduction or delay reasons.

14 Efficacy Analyses

Analysis set: FAS

There is no formal significance level for this study and all analyses are considered descriptive.

14.1 Primary Endpoint Analysis

14.1.1 Primary Objective: Analysis of the Confirmed Best Overall Response (BOR)

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoint: Confirmed Best Overall Response (BOR)			
Primary (FAS)	Confirmed BOR rate, denoted as Objective Response Rate (ORR) and defined as the proportion of participants having achieved confirmed CR or PR as best overall response, according to RECIST v1.1 assessed by the Investigator	The confirmed ORR will be calculated along with the two-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).	Participants with missing data are considered as non-responders.

Analyses of BOR: additional information

Best overall response (BOR), per Investigator assessment, will be assessed based on reported overall timepoint responses at different evaluation time points from the start of study treatment until documented disease progression in accordance to RECIST v1.1, taking requirements for confirmation into account as detailed below. Only tumor assessments performed before the start of any subsequent anti-cancer therapies (including re-initiate treatment) will be considered in the assessment of BOR. 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. Clinical deterioration will not be considered as documented disease progression in the context of BOR/tumor response.

Disease Control Rate (DCR), per Investigator assessment, will be assessed as noted above for BOR. DCR is defined as the proportion of participants having reached a confirmed BOR of CR, PR, or SD according to RECIST 1.1. DCR will be calculated along with the two-sided 95% CI using the Clopper-Pearson method as noted in the statistical analysis method for the primary endpoint, confirmed ORR.

In the case of multiple dates of scans within the same tumor assessment, the earliest scan date will be used as the date of tumor assessment. The order to obtain the BOR is the following: CR, PR, SD, PD, NE. If a participant is missing the baseline tumor assessment and/or has no on-treatment tumor assessments, BOR will be Not Evaluable (NE).

Table 1 summarizes the derivation rules described by Eisenhauer, et al (2009) for the BOR when confirmation from subsequent assessment is needed.

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) $\geq$ 6 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) $\geq$ 6 weeks after start date (and not qualifying for CR or PR).
- PD = progression $\leq$ 18 weeks after start date (and not qualifying for CR, PR or SD).
- Not Evaluable (NE) = all other cases.

SD can follow PR only in the rare case that the 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.

Table 1 BOR when confirmation of CR/PR is required

Overall response first time point	Overall response subsequent time point[a]	Confirmed BOR
CR	CR	CR
CR	PR	SD, if minimum criteria for SD duration met at first time point. Otherwise PD
CR	SD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD.
CR	PD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD.
CR	NE	SD, if minimum criteria for SD duration met at first time point. Otherwise NE.
PR	CR	PR
PR	PR	PR
PR	SD	SD, if minimum criteria for SD duration met at subsequent time point. Otherwise NE
PR	PD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD.
PR	NE	SD, if minimum criteria for SD duration met at first time point. Otherwise NE.
NE	NE	NE

[a] Subsequent time point is not necessarily the direct subsequent scan (e.g. PR-SD-PR will have PR as confirmed BOR).

A swimmer plot displaying key radiological milestones will be produced. For each participant, the time from treatment start until end of follow-up will be represented (from treatment start to last date known to be alive or date of death). In addition, the following information will be displayed: time to confirmed BOR (CR or PR), time to progression, and status at the end of the follow-up (alive or dead).

Participants with a BOR of NE will be summarized by reason for having NE status and displayed in a listing with relevant data. The following reasons will be used:

- No post-baseline assessments
- 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 start date without further evaluable tumor assessment)
- PD too late (>18 weeks after start date)

Time point tumor response and BOR will be presented in a listing.

14.1.2 Sensitivity Analyses of Confirmed BOR

The analyses noted in Section 14.1.1 will also be performed on certain subsets of participants from the FAS:

- Excluding those who discontinued cisplatin treatment due to toxicity without switching to carboplatin.
- Including only those who started treatment at least 18 weeks prior to local onset of the COVID-19 pandemic. The date of local onset for each country is defined as the minimum of the first death date per country as reported by the European Centre for Disease Prevention and Control, or 11-Mar-2020. The 18 weeks would have allowed each participant to have completed two tumor scans prior to the local onset of the COVID-19 pandemic.
- Including only those who had at least two post-baseline tumor assessments, or experienced progressive disease (PD) or death by the time of the second scheduled post-baseline assessment.

Each sensitivity analysis will be completed only if >5% of participants from the FAS would be excluded; otherwise, a sensitivity analysis is not expected to lead to different conclusions, and the impact could be examined on the subject level.

14.1.3 Subgroup Analyses of Confirmed BOR

Subgroup analyses will be performed on the primary endpoint for all subgroup levels defined in Section 8.2 "Subgroup definition and parameterization".

In addition, there will be a subgroup analysis of the patients dropping off of cisplatin, comparing those who switched to carboplatin and those who did not.

All the subgroup analyses will be exploratory; no adjustment for multiplicity will be performed. In the case of a low number of participants within a category (<5% of the population), the categories will be pooled when meaningful.

Frequency of confirmed BOR, percentage, and 95% CI of confirmed BOR will be estimated for all the subgroup analyses on BOR and presented in a forest plot. CIs will be based on exact Clopper-Pearson method.

Subgroup information and BOR will be presented in a data listing.

14.2 Secondary Endpoint Analysis

14.2.1 Secondary Endpoints

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods
Secondary Endpoint: Progression Free Survival (PFS)		
Secondary (FAS)	PFS, defined as the time (in months) from first treatment day to the date of the first documentation of objective disease progression (PD) according to RECIST v1.1 assessed by Investigator, or death due to any cause, whichever occurs first.	Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including median time with two-sided 95% CIs. In particular, the survival rate at 3, 6, and 12 months will be estimated with corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and CIs for the survival function estimates at above defined timepoints will be derived using the log-log transformation according to Kalbfleisch and Prentice (conftype=loglog default option in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula.
Secondary Endpoint: Overall Survival (OS)		
Secondary (FAS)	OS, defined as the time (in months) from first treatment day to the date of death due to any cause.	The analysis of OS will be performed with the Kaplan-Meier method with the same approach as for PFS. Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including corresponding two-sided 95% CIs. In particular, the proportion of OS at 6, 12, 18, and 24 months will be estimated with corresponding two-sided 95% CIs.
Secondary Endpoint: Duration of Response (DOR)		
Secondary (FAS)	DOR, defined for participants with confirmed CR or PR, as the time from first documentation of confirmed response to the date of first documentation of PD according to RECIST v1.1 (assessed by Investigator) or death due to any cause. The definition of the end of duration of response is consistent with the definition of end of PFS.	The analysis of DOR will be performed with the Kaplan-Meier method with the same approach as for PFS. Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including corresponding two-sided 95% CIs. In particular, the proportion of DOR at 6 and 12 months will be estimated with corresponding two-sided 95% CIs.

Analyses of progression free survival time and duration of response: additional information

Table 2 Outcome and event dates for PFS and duration of response analyses

Scenario	Date of event/censoring	Outcome
No baseline assessment	Date of first dose	Censored [a]
No post-baseline assessment	Date of first dose	Censored [a]
Progression or death ≤ 18 weeks after last tumor assessment or ≤ 18 weeks after date of first dose	Date of progression or death	Event
Progression or death > 18 weeks after the last tumor assessment	Date of last adequate assessment documenting no PD before subsequent anti-cancer therapy is given or missed assessments	Censored
No progression	Date of last adequate assessment documenting no PD before subsequent anti-cancer therapy is given or missed assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer medication given before PD	Date of last adequate assessment documenting no PD before subsequent anti-cancer therapy is given or missed assessments	Censored

[a] However if the patient dies ≤18 weeks after initial dose the death is an event with date of death

PFS time = (date of PD or death/censoring - date of first dose + 1)/30.4375 (months).

For imputing missing parts of dates of death, the rules defined in Section 9 will be used. In all other cases missing or incomplete dates will not be imputed. Progression dates are expected to be reported as complete dates.

Kaplan-Meier plots of PFS time and listing of PFS will be provided as well.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented. Censoring reasons are as follows:

- Ongoing in the study without an event (PD or death)
- No baseline assessment
- No post-baseline assessment
- No documented PD and death more than 18 weeks after last evaluable tumor assessment
- Start of new anti-cancer therapy

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

DOR = (date of PD or death/censoring – date of first documented objective response + 1)/30.4375 (months).

A listing with pertinent DOR information will be provided.

Analyses of overall survival time: additional information

Table 3 Date of event / censoring definition for OS analysis

Survival Status		Source	Censoring	Date of event/censoring
Died	Before cut-off	Death eCRF	Event	Date of death
	After cut-off	Death eCRF	Censored	Date of cut-off
Alive (no date of death)	Alive after cut-off	Follow-up eCRF	Censored	Date of cut-off
	Otherwise	Any documented assessment or data collected from an actual examination (details below)	Censored	Last date known to be alive

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

- All participant assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments, quality of life assessments)
- Start and end dates of anti-cancer therapies administered after study intervention discontinuation
- AE start and end dates
- Last known alive date collected on the "Survival information" eCRF page
- Study intervention start and end dates where dose is >0
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up)

Only dates associated with actual examinations of the participant reported in the eCRF will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last know alive date.

The Kaplan-Meier (KM) plots of OS time and listing of OS will be provided as well.

Frequency (number and percentage) of patients with an event (death) and censoring reasons will be presented. Censoring reasons are as follows:

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

Lost to follow-up will include the following participants:

- Lost to follow-up status is collected on the "Study Termination" or "End of Assessment Visit" eCRF page prior to the analysis cut-off;
- Participants with the last contact date > 13 weeks prior to the analysis cut-off date (duration of 13 weeks is based on the assessment schedule of every 12 weeks for survival follow-up interval + 1 week window).

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

The percent change in target lesions from baseline will be derived as:

- ((Sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline)* 100%

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments as:

- Minimum of ((sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) * 100%

The tumor shrinkage will be calculated based on investigator assessment. The percent change from baseline in target lesions per time point as well as other relevant information will be presented in a data listing. The percent change from baseline in target lesions as well as the first occurrence of new lesion and participant off treatment will be displayed against time point (months) in spider plots. The maximum reduction from baseline in the sum of target lesion diameters will be presented per participant in waterfall plots, color-coded in three separate plots by CCI [redacted], and CCI [redacted].

14.2.2 Sensitivity Analyses of Secondary Endpoints

The analyses noted in Section 14.2.1 will also be performed on the same subsets of the FAS as described in Section 14.1.2.

14.2.3 Subgroup Analyses of Secondary Endpoints

Subgroup analyses will be performed on PFS for all subgroup levels defined in Section 8.2 "Subgroup definition and parameterization".

All the subgroup analyses will be exploratory; no adjustment for multiplicity will be performed. In the case of a low number of subjects within a category (<10% of the population), the categories will be pooled when meaningful.

The same statistics will be provided for the subgroup analyses on PFS as those described in Section 14.2.1. CCI [redacted]

Subgroup information and PFS will be presented in a data listing.

CCI

[redacted]

15 Safety Analyses

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

Analysis set: SAF

15.1 Adverse Events

Definitions

Treatment-emergent adverse events (TEAEs): those events with onset dates occurring within the on-treatment period as defined in Section 9.

All analyses described in Section 15.1 will be based on TEAEs if not otherwise specified.

The listing for all AEs (whether treatment-emergent or not) will include all the data fields as collected on the "Adverse Events Details" eCRF page. A separate listing will also be provided for AEs that started after the on-treatment period, as well as a listing of AEs attributed to the impact of COVID-19.

Missing data handling

Incomplete AE-related dates will be handled as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study intervention then the onset date will be replaced by the minimum of start of study treatment and AE resolution date.
- In all other cases, the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the later case, the date of death will be used to impute the incomplete stop date.
- In all other cases, the incomplete stop date will not be imputed. If stop date of AE is after date of cut-off, outcome of AE is ongoing at cut-off.
- Further information after cut-off (like fatal outcome) might be taken from Safety database and included separately into the CSR.

The following categories of TEAEs are defined for reporting:

Related Adverse Events: adverse events with relationship to study treatment (as recorded on the AE eCRF page: Relationship with Avelumab, Cetuximab, Cisplatin, Carboplatin, or Gemcitabine = Related) reported by the Investigator and those of unknown relationship (i.e., no answer to the question "Relationship with study treatment"). Unless specified per treatment, AEs related to study treatment will be defined as any AE considered related to any study treatment.

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

Adverse Events Leading to Treatment Discontinuation: adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with Avelumab, Cetuximab, Cisplatin, Carboplatin, or Gemcitabine = Drug withdrawn).

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

Immune Related Adverse Events (irAEs): irAEs are identified based on a list of MedDRA PTs and other criteria as specified in Table 6 of Appendix I.

Infusion Related Reactions (IRRs): IRRs are identified based on a list of MedDRA PTs. The detailed criteria of the timing relationship to infusion are specified in Table 6 of Appendix I.

Unless otherwise specified, AEs will be displayed in terms of frequency tables in alphabetical order by primary SOC and PT. If an AE is reported for a given participant more than once during treatment, the worst severity and the worst relationship to study treatment will be tabulated.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within an SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

15.1.1 All Adverse Events

AEs will be summarized by worst severity (according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0) per participant, using MedDRA PT as event category and MedDRA primary SOC as body system category.

In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following overall frequency tables will be prepared.

- Any TEAE
- Any study treatment related TEAEs*
- Any serious TEAEs
- Any study treatment related serious TEAEs*
- Any TEAE by NCI-CTCAE severity Grade ≥3
- Any study treatment related TEAE by NCI-CTCAE severity Grade ≥3*
- TEAEs leading to permanent treatment discontinuation
- Related TEAEs leading to permanent treatment discontinuation*
- Any TEAEs leading to death (TEAEs with Grade 5 or outcome "fatal" if Grade 5 not applicable)

- Any study treatment related TEAEs leading to death (TEAEs with Grade 5 or outcome "fatal" if Grade 5 not applicable)*
- Treatment-emergent irAEs
- Related treatment-emergent irAEs*
- Treatment-emergent IRRs
- Related treatment-emergent IRRs*

In addition the tables will be provided by PT and primary SOC in alphabetical order:

- TEAEs by SOC and PT and worst grade
- Related TEAEs by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT
- TEAEs by SOC and PT: displaying in separate columns the All TEAEs / Related TEAEs / Grade ≥3 TEAEs / Related Grade ≥3 TEAEs

Categories annotated by * will be further summarized for each study drug (i.e., avelumab, cetuximab, cisplatin, carboplatin, and gemcitabine) as part of the overview frequency table.

Clinical trial.gov and EudraCT -requirements

Summary tables for non-serious adverse events excluding SAEs applying frequency threshold of 5% will be provided. The non-serious AEs are not restricted to non-serious TEAEs.

15.1.2 Adverse Events Leading to Treatment Discontinuation

The following overall frequency tables will be provided.

Drug Interrupted

- Any TEAEs leading to drug interruption*
- Any study treatment related TEAEs leading to drug interruption*

Permanent discontinuation

- Any TEAEs leading to permanent discontinuation*
- Any study treatment related TEAEs leading to permanent discontinuation*
- Avelumab related TEAEs leading to study drug discontinuation
- irAEs leading to permanent Avelumab discontinuation
- IRRs leading to permanent Avelumab discontinuation
- IRRs leading to permanent Cetuximab discontinuation

The following summaries by SOC and PT will be produced:

- TEAEs leading to permanent treatment discontinuation*
- Treatment related AEs leading to permanent treatment discontinuation*

Categories annotated by * will be further summarized for each study drug (i.e., avelumab, cetuximab, cisplatin, carboplatin and gemcitabine).

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

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

15.2.1 Deaths

Death summarization will be tabulated based on information from the "End of Assessment Visit", each study drug "Termination", "Subject Status / Survival Follow-Up", "Study Termination", and "Death" eCRF pages.

- Number and percentage of participants who died
- Primary reason for death
  - Disease progression
  - Adverse event related to study treatment
  - Adverse event not related to study treatment
    - Covid 19
  - Other
  - Unknown
- Number and percentage of participants who died within 30 days of the last study treatment administration
- Primary reason for death
  - Disease progression
  - Adverse event related to study treatment
  - Adverse event not related to study treatment
    - Covid 19
  - Other
  - Unknown
- Number and percentage of participants who died within 60 days of the first study treatment administration

- Primary reason for death
  - Disease progression
  - Adverse event related to study treatment
  - Adverse event not related to study treatment
    - COVID-19
  - Other
  - Unknown

In addition, date and cause of death will be provided in individual subject data listing together with selected dosing information and will include the following information:

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

15.2.2 Serious Adverse Events

Please refer to Section 15.1.1 for serious adverse event (SAE) related outputs. The frequency (number and percentage) of subjects with each of the following will be presented for treatment-emergent SAEs:

- SAEs by SOC and PT
- Related SAEs by SOC and PT

The listings of SAEs will also be provided with relevant information such as AE SOC/PT, start/stop date, toxicity grade, relationship to each study drug, action taken with each study drug, and outcome.

15.2.3 Other Significant Adverse Events

15.2.3.1 Infusion Related Reaction

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

- IRRs leading to death, by PT
- Related IRRs leading to death, by PT
- IRRs, by PT
- IRRs, Grade ≥ 3, by PT
- Related IRRs, by PT
- Related IRRs, Grade ≥ 3, by PT

- IRRs leading to permanent treatment discontinuation, by PT
- Related IRRs leading to permanent treatment discontinuation, by PT
- Serious IRRs, by PT
- Related serious IRRs, by PT
- Time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later)

The listing of all IRRs will also be provided with the relevant information.

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.

15.2.3.2 Immune Related Adverse Event

The following tables will be created for treatment-emergent irAEs, as identified by the Investigator on the AE eCRF page.

- The frequency (number and percentage) of subjects with each of the following will be presented for treatment emergent irAEs:
  - All irAEs
  - Serious irAEs
  - irAEs, grade ≥ 3
  - irAEs leading to permanent treatment discontinuation*
  - irAEs leading to death
- irAEs leading to death, by SOC and PT
- irAEs by SOC and PT
- irAEs, grade ≥ 3, by SOC and PT
- irAEs leading to permanent discontinuation of any study treatment by SOC and PT
- irAEs by SOC, PT, and worst grade

Categories annotated by * will be further summarized for each study drug (i.e., avelumab, cetuximab, cisplatin, carboplatin, and gemcitabine) as part of the overview frequency table.

The listing of all irAEs will also be provided with all relevant information including a flag for irAEs with onset outside of the on-treatment period. The following information will be provided for each irAE:

- The time from first treatment of avelumab to start of irAE
- The time from most recent treatment of avelumab until start of irAE
- The duration of the irAE

15.3 Clinical Laboratory Evaluation

Analysis set: SAF

15.3.1 Hematology and Chemistry Parameters

Laboratory results will be classified according to the NCI-CTCAE Version 5.0 as provided by the central or local laboratory. Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limits, within normal limits and above normal limits (according to the laboratory normal ranges). Please see Appendix II for a list of the CTCAE-gradable parameters.

The worst on-treatment grade will be summarized considering only participants with post baseline laboratory samples: Laboratory tests by NCI-CTCAE grade (0, 1, 2, 3, 4, any).

Quantitative data will be examined for trends using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline to each visit over time. The changes computed will be the differences from baseline. End of Treatment visit will be summarized separately. Qualitative data based on reference ranges will be described according to the categories (i.e. Low, Normal, and High). The number of participants with clinical laboratory values below, within, or above normal ranges at baseline compared to endpoint will be tabulated for each test. Shift tables of baseline versus the worst value at any post-baseline visit will be presented.

Abnormalities classified according to NCI-CTCAE toxicity grading version 5.0 will be described using the worst grade. For those parameters which are graded with two toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g., hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa.

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

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

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

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

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

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

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

NCI-CTCAE grades available:

- Number and percentage of participants with any, NCI-CTC grade 0, 1, 2, 3, 4, 3 or 4 laboratory abnormalities during the on-treatment period – (worst case)
- Shifts in toxicity grading baseline to worst on-treatment CTCAE grade

NCI-CTCAE grades not available:

- Number of participants with shifts baseline normal to at least one result above normal on-treatment
- Number of participants with shifts baseline normal to at least one result below normal on-treatment

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges.

Baseline (Week 0) is the last measurement prior to the first dose of any study intervention.

Participants without post-baseline laboratory samples will be excluded from analyses with respect to values after baseline.

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

ALT: ≥3×ULN / ≥5×ULN / ≥10×ULN / ≥20×ULN.

AST: ≥3×ULN / ≥5×ULN / ≥10×ULN / ≥20×ULN.

(ALT or AST): ≥3×ULN / ≥5×ULN / ≥10×ULN / ≥20×ULN.

Total bilirubin: ≥2×ULN.

ALT ≥3×ULN concurrently with total bilirubin ≥2×ULN.

AST ≥3×ULN concurrently with total bilirubin ≥2×ULN.

(ALT or AST) ≥3×ULN concurrently with total bilirubin ≥2×ULN.

(ALT or AST) ≥3×ULN concurrently with total bilirubin ≥2×ULN and ALP >2×ULN.

(ALT or AST) ≥3×ULN concurrently with total bilirubin ≥2×ULN and ALP ≤2×ULN or missing.

Concurrent measurements are those occurring on the same date.

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

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, by graphically displaying

peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT >3×ULN and total bilirubin >2×ULN;

peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST >3×ULN and total bilirubin >2×ULN.

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with a post-baseline TBILI ≥ 2×ULN, ALT≥ 3×ULN or AST ≥ 3×ULN will be provided.

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.

- Coagulation: aPTT, prothrombin time INR
- Urinalysis: all urinalysis parameters
- Other parameters: such as immunology, soluble factor
- Pregnancy test
- Serology
- Hormones: free thyroxine and thyroid-stimulating hormone

15.4 Vital Signs

Analysis set: SAF

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

All vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each visit over time. End of treatment visit will be summarized separately. The changes computed will be the differences from baseline.

The maximum changes of vital sign measurements from screening/baseline to on-treatment values will be grouped as follows:

Table 4 Vital Sign Maximum Change Categories

Body temperature increase	*< 1℃ , 1-<2℃ , 2-<3℃, ≥ 3 ℃*
Weight increase	*<10%, ≥ 10%*
Weight decrease	*<10%, ≥ 10%*
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*

bpm=beats per minute for heart rate and breaths per minute for respiration rate; DBP=diastolic blood pressure; SBP=systolic blood pressure.

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) from baseline
- Listing of highest change per participant

An additional participant data listing will present all changes from baseline reported in the highest categories.

15.5 Other Safety or Tolerability Evaluations

15.5.1 ECG

The 12-lead Electrocardiogram (ECG) assessment will be performed during screening (baseline) and at the Discontinuation / End-of-Treatment visit. For each of the ECG parameters, descriptive statistics at baseline and at the Discontinuation / End-of-Treatment visit and changes from baseline will be presented.

The incidence and percentage of participants with the worst potentially clinically significant abnormalities (PCSA) for ECG parameters will be summarized during the on-treatment period. Each participant will be counted only once within each category. As ECG assessments are only performed during screening and at the Discontinuation/End-of-Treatment visit, the denominator

to calculate percentages for each PCSA category is the number of participants with a Discontinuation/End of Treatment visit. The PCSA criteria are provided in Table 5 below.

Table 5 Potentially Clinically Significant Abnormalities criteria for ECG

Test	Potentially Clinically Significant Abnormalities (PCSA) Criteria
Heart Rate	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm
PR Interval	≥ 220 ms and increase from baseline ≥ 20 ms
QRS	≥ 120 ms
QT Interval	Interval >450 ms and interval ≤ 480 ms Interval >480 ms and interval ≤ 500 ms Interval >500 ms
QT Interval	Increase from baseline > 30 ms and ≤ 60 ms Increase from baseline > 60 ms

A listing of abnormal 12-lead ECGs will be provided with all relevant information and derived variables.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline. However, they will be used in the analysis of notable ECG changes.

15.5.2 ECOG Performance Status

The ECOG shift from baseline to highest score during the on-treatment period will be summarized. ECOG performance status with shift from ECOG=0 or 1 to ECOG=2 or higher will also be presented in a data listing with subject identifier and other relevant information.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

The analyses described in this section will be performed by the Clinical PK/PD Group, Merck Healthcare KGaA, Darmstadt, Germany, or by a Contract Research Organization (CRO) selected by the Sponsor.

Analysis will be provided for the SAF and PKAS, respectively.

16.1.1 Missing/non-quantifiable PK Data Handling

Concentrations below the lower limit of assay quantification

Pharmacokinetic concentrations below the lower limit of quantification (BLQ) are set to zero for calculating parameters and descriptive statistics.

Deviations, missing concentrations, and anomalous values

There will be no imputation of missing data. Concentrations will be set to missing in summary tables if the value is reported as no result.

Pharmacokinetic concentrations which are erroneous due to a protocol violation (as defined in the clinical study protocol and/or Section 10.2), documented handling error, or analytical error (as documented in the protocol deviation log, bioanalytical data, and/or bioanalytical report) may be excluded from the PK analysis if agreed upon prior to performing a statistical analysis. In this case the rationale for exclusion must be provided in the CSR. Any other PK concentrations that appear implausible to the Pharmacokineticist/PK/PD Data Analyst must not be excluded from the analysis. Any implausible data will be documented in the CSR.

If an individual participant has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level), this participant/value will be excluded from the descriptive statistics and instead the result will be listed only.

Relevant decisions on participant inclusion in the PK analysis set will be made before database lock in the Database Review Meeting (DRM).

16.1.2 Descriptive PK Analysis

Presentation of PK Concentration Data

Listings

Individual PK sample times, time deviations, and concentration data will be listed by participant, study day, and nominal time. Concentration listings will be based on the SAF. Pharmacokinetic concentrations will be reported with the same precision as the source data provided by the bioanalytical laboratory. Actual elapsed sample collection times will be rounded to two decimal places with units of hours for reporting purposes in listings.

Tables

Pharmacokinetic concentration data will be presented for both compounds (Avelumab and Cetuximab) in tables and descriptively summarized for the PKAS, by study day and nominal time using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (StdDev), coefficient of variation (CV%), minimum (Min), median (Median), and maximum (Max).

Summaries of pre-dose and end-of-infusion concentrations other than first dosing interval will be covered by the parameter summaries only.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data provided by the bioanalytical laboratory 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

StdDev: 4 significant digits

CV%: 1 decimal place

Figures

Individual PK concentration-time profiles showing all participants will be created using the actual time points and the numeric concentration data. Arithmetic mean and median concentration-time profiles will be provided using scheduled (nominal) time points and the numeric concentration data. All concentration-time plots for PK data will be presented both on a linear and on a semi-logarithmic scale. Mean PK plots will include StdDev error bars when plotted on a linear scale. Individual data will be presented based on the SAF, and summaries will be based on the PKAS.

Figures of Ceoi (concentration at end-of-infusion) and Ctrough (concentrations immediately before next treatment other than first dosing interval) will be covered by the parameter summaries only.

16.1.3 Pharmacokinetic Parameter Analysis

Presentation of PK Parameter Data

Listings

Individual PK parameter data (Ceoi and Ctrough) will be listed for both compounds (Avelumab and Cetuximab) by participant and study day. Parameter listings will be based on the SAF. Pharmacokinetic parameters will be reported to 3 significant digits in listings.

Tables

Pharmacokinetic parameter data (Ceoi and Ctrough) will be presented in tables and descriptively summarized for the PKAS for both compounds (Avelumab and Cetuximab) by study day using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (StdDev), coefficient of variation (CV%), minimum (Min), median (Median), maximum (Max), geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%), and the 95% confidence interval for the GeoMean (LCI 95% GM: lower 95% CI for GeoMean, UCI 95% GM: upper 95% CI for GeoMean).

In export datasets, as well as in the SDTM PP domain, PK parameters will be provided with full precision and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values and rounded for reporting purposes only.

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

Mean, Min, Median, Max, GeoMean, 95% CI: 3 significant digits

StdDev: 4 significant digits

CV%, GeoCV%: 1 decimal place

The PK parameters listed below will be calculated for Avelumab and Cetuximab and be analyzed with the same precision as the source data provided by the bioanalytical laboratory.

C_{eoi}	The concentration observed immediately at the end of infusion. This will be taken directly from the observed Avelumab or Cetuximab concentration-time data.
C_{trough}	The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing). This will be taken directly from the observed Avelumab or Cetuximab concentration-time data.

Figures

Individual PK trough concentration (C_{trough}) and end of infusion concentration (C_{eoi}) values will be plotted against actual study day on a linear scale, for all participants by part and treatment. Individual data will be presented based on the SAF.

Arithmetic mean (±StdDev) and median C_{trough} and C_{eoi} will be plotted versus nominal study day by part, and treatment on a linear scale. Summaries will be based on the PKAS.

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16.4 COVID-19 Impact

Analysis set: SAF

In addition to the sensitivity analyses described in Section 14, COVID-19 related impact on the planned trial procedures will be summarized based upon the eCRF pages related to disposition ('TTERM', 'STERM', and 'DEATH'), as well as the protocol deviations reported in CTMS with the coding prefix 'COVID-19'. The summary will include:

- Total number of occurrences, as well as number of unique participants, with any COVID-19 related protocol deviation
    - Missed visits overall (total number and unique participants)
    - Missed efficacy evaluations (total number and unique participants)
    - Missed dosing visits (total number and unique participants)
- Number of participants who discontinued any study treatment for any reason related to COVID-19
- Number of participants who discontinued the study for any reason related to COVID-19
- Number of participants with cause of death related to COVID-19

17 References

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CCI [redacted]

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18 Appendices

18.1 Appendix I – Description of the Case Definition for Assessment of irAEs and IRRs

irAEs

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

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

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

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

4a) On the AE eCRF page, the question, "Does any of the following provide a clear etiology for the event?" has "No" selected or is left blank

OR

4b) On the AE eCRF page, the question, "Is the histopathology or biopsy consistent with an immune-mediated event?" has "Yes" selected.

IRRs

Infusion related reactions are identified based on a list of MedDRA PTs and criteria on the timely relationship according to Table 6.

Table 6 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 • Dizziness • Loss of consciousness or shock

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

NCI-CTC gradable parameters

Category	Parameter	Name in NCI-CTC	Direction(s) of abnormality
	Serum chemistry		
Electrolytes	Corrected Calcium	Hypocalcemia/Hypercalcemia	Low/High
Electrolytes	Magnesium	Hypomagnesemia/Hypermagnesemia	Low/High
Electrolytes	Potassium	Hypokalemia/Hyperkalemia	Low/High
Electrolytes	Sodium	Hyponatremia/Hypernatremia	Low/High
Enzymes/cardial	Creatinine Phosphokinase	CPK increased	High
Enzymes/cardial	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	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

NCI-CTC non-gradable parameters

Category	Parameter (LBTEST)	Direction(s) of abnormality
	Serum chemistry	
Electrolytes	Calcium	High/Low
Electrolytes	Chloride	High/Low
Electrolytes	Phosphate	Low
Metabolism	Glucose	High
Plasma proteins	Total protein	Low
Plasma proteins	C Reactive protein	High
Renal/kidney	Urea	High
Renal/kidney	Blood Urea Nitrogen	High
	Hematology	
Red blood cells	Hematocrit	High/Low
Red blood cells	Red blood cells (Erythrocytes)	High/Low
White blood cells/differential	Basophils	High
White blood cells/differential	Monocytes	High/Low

ELECTRONIC SIGNATURES

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Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	PPD	Technical Approval	PPD
PPD	PPD	Business Approval	PPD