# Integrated Analysis Plan

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| **Clinical Study Protocol Identification No.** | MS202202_0002 |
| **Title** | A Phase II single-arm study to investigate tepotinib combined with cetuximab in *RAS/BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) patients having acquired resistance to anti-EGFR antibody targeting therapy due to *MET* amplification |
| **Study Phase** | II |
| **Investigational Medicinal Product(s)** | Tepotinib in combination with cetuximab |
| **Clinical Study Protocol Version** | 27 April 2020/Version 1.0 |
| **Integrated Analysis Plan Author** | **Coordinating Author**<br>PPD, Merck KGaA — PPD<br>**Function** — **Author(s) / Data Analyst(s)**<br>PPD — PPD<br>PPD, Merck KGaA |
| **Integrated Analysis Plan Date and Version** | 10 Mar 2021 / Version 1.0 |
| **Integrated Analysis Plan Reviewers** | **Function** — **Name**<br>PPD — PPD<br>PPD<br>PPD, Merck KGaA<br>PPD, Merck KGaA<br>Medical Lead, Merck KGaA<br>PPD, Merck KGaA<br>PPD, Merck KGaA — PPD<br>PPD, Merck KGaA<br>PPD, Merck<br>PPD, Merck KGaA<br>PPD, Merck KGaA<br>PPD, Merck<br>PPD, Merck KGaA<br>PPD, Merck KGaA<br>PPD m<br>PPD Merck KGaA<br>Clinical Trial Lead, EMD Serono — PPD |

# Approval Page

**Integrated Analysis Plan:** MS202202_0002

A Phase II single-arm study to investigate tepotinib combined with cetuximab in *RAS/BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) patients having acquired resistance to anti-EGFR antibody targeting therapy due to *MET* amplification.

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

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

# 1 Table of Contents

# 2 List of Abbreviations and Definition of Terms

| | |
|---|---|
| 2L | 2nd Line |
| 3L+ | 3rd Line + |
| ACCRU | Academic and Community Cancer Research United |
| ADA | Anti-Drug Antibody |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALP | Alkaline phosphatase |
| ALT | Alanine transaminase |
| AST | Aspartate transaminase |
| ATC | Anatomical Therapeutic Chemical classification |
| BMI | Body Mass Index |
| BOR | Best Overall Response |
| BSA | Body Surface Area |
| BUN | Blood Urea Nitrogen |
| CDISC | Clinical Data Interchange Standards Consortium |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| COVID-19 | Coronavirus disease 2019 |
| CR | Complete Response |
| (e)CRF | (electronic) Case Report Form |
| CSR | Clinical Study Report |
| CTMS | Clinical Trial Management System |
| CV | Coefficient of variation |
| DLT | Dose Limiting Toxicity |
| DoR | Duration of Response |
| ECG | Electrocardiogram |
| ECOG | Eastern Co-operative Oncology Group |
| EGFR | Epidermal growth factor receptor |
| FAS | Full Analysis Set |
| FLC | Free Light Chain |
| FU | Follow-up |

| | |
|---|---|
| GFR | glomerular filtration rate |
| ICH | International Conference on Harmonization |
| IAP | Integrated Analysis Plan |
| ICH | International Conference on Harmonization |
| IPD | Important Protocol Deviation |
| IRC | Independent Review Committee |
| LLN | Lower Limit of Normal |
| LLOQ | Lower limit of quantification |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic Resonance Imaging |
| NA | Not Applicable |
| NCI-CTCAE | National Cancer Institute – Common Terminology Criteria for Adverse Events |
| OR | Objective Response |
| ORR | Objective Response Rate |
| PD | Progressive Disease |
| Pd | Pharmacodynamics |
| PFS | Progression Free Survival |
| PR | Partial Response |
| PT | Preferred Term |
| PK | Pharmacokinetics |
| PP | Per Protocol |
| QD | Once Daily |
| PR | Partial Response |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RP2D | Recommend Phase II Dose |
| SAE | Serious Adverse Event |
| SAF | Safety |
| SCR | Screening analysis population |
| SD | Stable Disease |
| StDev | Standard Deviation |

| | |
|---|---|
| SDTM | Study Data Tabulation Model |
| SI | International System of Units |
| SMC | Safety Monitoring Committee |
| SOC | System Organ Class |
| TEAE | Treatment-Emergent Adverse Event |
| 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 | 10 Mar 2021 | PPD | First version |
| | | | |

# 4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for all the analyses of data collected for protocol MS202202_0002.

Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR) or in separate reports. Additionally, the planned analyses identified in this IAP may 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 Protocol version 1.0 dated 27 April 2020 and is prepared in compliance with ICH E9. It describes analyses planned in the protocol.

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

# 5 Objectives and Endpoints

## Safety Run-in

| Objectives | Endpoints (Outcome Measures) | IAP section |
|---|---|---|
| **Primary** | | |
| To confirm the recommended Phase II dose (RP2D) of tepotinib when used in combination with cetuximab | Occurrence of dose limiting toxicities (DLTs) | Section 15.1 |

## Overall Study

| Objectives | Endpoints (Outcome Measures) | IAP section |
|---|---|---|
| **Primary** | | |
| To evaluate the preliminary efficacy of tepotinib (RP2D) in combination with cetuximab in terms of tumor response | Objective response (OR, confirmed complete response [CR] or partial response [PR]) determined according to RECIST Version 1.1 assessed by the Investigators | Section 14.1 |
| **Secondary** | | |
| To further evaluate the efficacy of the combination of tepotinib (RP2D) and cetuximab in terms of | | |
| duration of response (DoR) | DoR (months) according to RECIST Version 1.1 assessed by the Investigators. | Section 14.2.1 |
| progression-free survival (PFS) | PFS (months) according to RECIST Version 1.1 assessed by the Investigators. | Section 14.2.2 |
| overall survival (OS) | OS (months) assessed by the Investigators. | Section 14.2.3 |
| To evaluate the safety and tolerability of tepotinib in combination with cetuximab | • Occurrence of Adverse Events (AE) and treatment-related AEs<br>• Occurrence of clinically significant changes in vital signs, laboratory parameters and 12-lead electrocardiogram (ECG) findings | Section 15 |
| To characterize the immunogenicity of cetuximab | Immunogenicity of cetuximab as measured by antidrug antibody (ADA) assays on Day 1 Cycle 1 and End of Treatment Visit | Section 14.2.4 |
| CCI [redacted] | | |

| Objectives | Endpoints (Outcome Measures) | IAP section |
|---|---|---|
| CCI | | |

# 6 Overview of Planned Analyses

This IAP covers the analyses for efficacy, safety, CCI and CCI data to be performed for the primary and final analyses. More details about each ecific analysis are provided in the subsections below.

Statistical analyses will be performed on the basis of CDISC SDTM data. These SDTM data contain as clean as possible eCRF data as well as external data including laboratory data, biomarker data, and tumor assessment results by Investigator.

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

## 6.1 Analyses for SMC meetings

The primary safety endpoint (i.e. the occurrence of DLTs during the first treatment cycle of the safety run-in period) will be evaluated during SMC meetings and based on participant profiles. More details are provided in the SMC Charter.

The Safety Monitoring Committee (SMC) will decide on dose escalation, dose de-escalation, expansion of the current dose level, or suspension of enrollment based on safety and, if available, PK data. In the safety run-in period, at least 6 treated participants on a dose level are regarded as necessary to confirm the RP2D of tepotinib. Cohorts of 3 participants will be enrolled. SMC meetings will take place after 3 treated participants within a dose-specific cohort completed the first cycle. On request additional SMC meetings might take place. Participants who are not DLT evaluable will be replaced. Once all participants of the respective dose-specific cohort have completed the DLT period or discontinued from trial prematurely, a data snapshot will be taken for provision of SMC participant profiles. There will be no data cut-off applied.

The SMC will decide and confirm the recommended Phase II dose (RP2D) of tepotinib to be used in combination with cetuximab. The SMC may also decide to reduce the tepotinib dose to 250 mg QD based on the data collected during the safety run-in and for the whole study.

## 6.2 Interim analysis for futility

A futility analysis will be performed after the first 12 participants are enrolled for second line (2L) treatment (Cohort A). The date 13 weeks after the first dose date (the scheduled time point of the second scan, C5D1, including a time window of 7 days) of the 12$^{th}$ patient enrolled will be used here as cut-off date. Recruitment of further participants into this study, both cohorts, will continue. If there are less than 2 responders (confirmed CR or PR) within the first 12 participants treated with RP2D, the enrolment of 2L participants for this study might be stopped for futility.

## 6.3 Primary analysis

The primary analysis will be the main analysis that is planned around 5 months after last participant first dose.

## 6.4 Final analysis

The final analysis will be performed after end of study. An extract of the primary analysis as specified in the table of contents for TFLs will be created for the follow-up analysis after database lock.

# 7 Changes to the Planned Analyses in the Clinical Study Protocol

## 7.1 COVID-19 Impact

No changes to the planned analysis of the efficacy or safety endpoints are planned due to the impact of Coronavirus disease 2019 (COVID-19) outbreak. Sensitivity analyses may be considered depending on the observed COVID-19 findings.

Additional outputs (summary table and listing) will be generated for a description of the impact by COVID-19 on the study. The number and percentage of participants will be presented for the following findings due to COVID-19:

- Potentially affected by COVID-19
- Adverse Events
- Protocol deviations (important and non-important)
- Missed Visits (including number of missed visits)
- Missed efficacy evaluations (including number of missed efficacy evaluations)
- Tele-visits performed (including number of tele-visits)
- Drug administration - missed doses

- Drug administration - dose adjustments
- Laboratory testing performed by external laboratory unit (only if at least 10 participants are affected)
- Treatment discontinuation (of cetuximab and/or tepotinib)
- Study discontinuation
- Death

Potentially affected participants (either due to infection or due to circumstances of social distancing affecting the capabilities of sites/hospitals etc.) are defined as:

a) Participants who started treatment after start of the COVID-19 pandemic, or

b) Participants who started treatment prior to start of the COVID-19 pandemic and had tumor assessments planned after the start of the pandemic (i.e., did neither have progressive disease, died or withdrew from tumor assessments prior to start of the pandemic).

A frequency table will be produced for the Safety Analysis Set to present the number of participants with important protocol deviations related to COVID-19 (categorized by frequency of participants with an important protocol deviation overall as well as by category of protocol deviation and type of protocol deviation). A separate table for the non-important protocol deviations related to COVID-19 (categorized by frequency of subjects with a non-important protocol deviation overall as well as by category of protocol deviation) will also be produced.

In addition, separate listings of COVID-19 related adverse events and protocol deviations will also be produced.

Outputs related to disposition and exposure will be amended to present reason of treatment/study discontinuations due to COVID-19 and treatment delays due to COVID-19 (if possible).

Laboratory results performed by external laboratory units will be included in the summary statistics and shift analyses, provided that normal ranges are not missing; if they are missing, results will be listed and included in summary statistics outputs only.

# 8 Analysis Populations and Subgroups

## 8.1 Definition of Analysis Populations

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.

**Screening Analysis Set (SCR)**

The Screening analysis set includes all participants, who provided informed consent, regardless of the participant's study intervention status in the study.

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

These analysis sets will include all participants, who were administered at least one dose of any study intervention.

### Dose Limiting Toxicity Analysis Set (DLT)

The Dose Limiting Toxicity analysis set (DLT) will include all participants who received at least one dose of study treatment in the safety run-in period and meet at least one of the following criteria:

- Received at least 75% of the tepotinib and cetuximab planned dose and complete the DLT period (3 weeks after start of treatment with study intervention).
- Experienced a DLT during the DLT period, regardless of the received amount of each study intervention.

### Pharmacokinetics Analysis Set (PKAS)

The pharmacokinetics analysis set will include all participants, who received at least one dose of study intervention, have no relevant protocol deviations or important events affecting PK, and provide at least one measurable post-dose concentration. Participants will be analyzed per the actual study intervention they received.

### Immunogenicity Analysis Set (IMAS)

All participants who receive at least one dose of study intervention and have at least one valid ADA result. Participants will be analyzed per the actual study intervention they received.

### Analyses per Analysis Set

The following table summarizes the use of the analysis sets in the different analyses.

| | Analysis Set | | | | |
|---|---|---|---|---|---|
| **Analyses** | **DLT** | **FAS** | **SAF** | **PK** | **IMAS** |
| DLT | ✓ | | | | |
| Baseline Characteristics | | ✓ | | | |
| Previous and Concomitant Therapies | | ✓ | | | |
| Compliance and Exposure | | | ✓ | | |
| Efficacy: Primary | | ✓ | | | |
| Efficacy: Secondary | | ✓ | | | |
| Safety and Tolerability | | | ✓ | | |
| PK | | | | ✓ | |
| Immunogenicity | | | | | ✓ |

DLT = Dose Limiting Toxicity; FAS = Full Analysis Set; SAF = Safety Analysis Set; PK = Pharmacokinetics; IMAS = Immunogenicity Analysis Set.

All safety analyses will be presented by cohort and dose level, if applicable. Efficacy analyses will be done by cohort and assigned dose level of tepotinib.

For more details see Section 0 General Specifications for Data Analyses.

## 8.2 Subgroup Definition and Parameterization

Subgroup analyses will be performed on the primary efficacy endpoint OR and the secondary efficacy endpoints DoR/PFS/OS as defined in Table 1. All subgroup analyses will be exploratory, no adjustment for multiplicity will be performed. Endpoints for which subgroup analyses will be performed can be found in Section 14. In case of low number of participants within a subgroup level (< 5 participants), levels will be pooled when meaningful.

For the definition of subgroup levels, data as documented in the electronic case report form (eCRF) or provided in the SDTM datasets will be taken. The category "missing" will not be included in any subgroup analysis.

**Table 1. Subgroups**

| Subgroup | Subgroup level | Definition/ Derivation |
|---|---|---|
| Treatment line | • 2nd line (Cohort A)<br>• 3rd line<br>• 4th line<br>• 5th + line | CRF: PRIOR ANTI-CANCER DRUG THERAPIES DETAILS: Regimen number |
| Site location<br>(Cohort B) | • ACCRU sites<br>• Other US sites | |
| Mutations in the extracellular domain of EGFR | • Yes<br>• No | The following mutations are of relevance and should be taken into account: F404, T414, V441, S442, I462, S464, G465, K467, K489, I491, S492 |
| MET amplification<br>(if available) | • Focal<br>• Non-focal | |
| MET amplification | • Liquid<br>• Tissue | CRF: TISSUE BIOPSY FOR MET |

| | | |
|---|---|---|
| | | AMPLIFICATION: MET amplification result |
| Prior EGFR therapy | • Panitumumab<br>• Cetuximab | |
| Time since last EGFR therapy in months | • 1<br>• 2<br>• > 2 | |
| HGF protein expression level<br>(if available) | • < median<br>• ≥ median | |
| Age group | • < 65 years<br>• ≥ 65 years | |
| Race | • White<br>• Black or African American<br>• Asian<br>• Not collected at this site<br>• Other | • White<br>• Black or African American<br>• Asian<br>• Other (including American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander)<br>"Not collected at this site" will be handled as missing |
| Sex | • Male<br>• Female | |
| Brain metastases at baseline | • Present<br>• Absent | |
| ECOG at baseline | • 0<br>• 1 | |

# 9 General Specifications for Data Analyses

This section describes any general specifications not included in subsequent sections.

**Study treatment and study treatment component:**

Participants will receive tepotinib (RP2D mg daily) in combination with cetuximab (loading dose (where required) 400 mg/m$^2$, followed by or starting with weekly infusions at a dose of 250 mg/m$^2$).

In this IAP, "study treatment" will be used to indicate the combination of tepotinib and cetuximab; "study treatment component" will be used to refer to tepotinib or cetuximab.

**Study treatment start date:**

For each participant, the "start date" of this study is the date of first administration of the study treatment. If, for any reason, the first administration of tepotinib and cetuximab does not happen on the same day, the date of administration of the first study treatment component taken should be considered as the "start date".

**Study treatment end date:**

The last tepotinib and cetuximab administration dates are collected on the "Tepotinib Termination" and "Cetuximab Termination" eCRF pages. These should be considered the dates of permanent discontinuation of tepotinib and cetuximab respectively.

The end of study treatment will be the last study tepotinib administration date or the last study cetuximab administration date, whichever comes later.

**Dose Level:**

As stated in Section 6.1, the SMC will decide whether the tepotinib 500 mg dose level is considered safe or if the 250 mg dose level should be used instead. Cetuximab will be administered as intravenous infusion as detailed in protocol Section 6.1.

**Cohort:**

Cohort A – includes participants outside of US for 2L treatment.

Cohort B – includes US participants for 3L+ treatment.

**Presentation of analysis results:**

Unless stated otherwise, for disposition, baseline characteristics (e.g. demographics, medical history, disease history, etc.), previous and concomitant medications and procedures, results will be presented by cohort, by assigned dose level of tepotinib and overall.

For efficacy analyses, results will be presented by cohort and assigned dose level of tepotinib.

Exposure and safety will be presented by cohort and dose level, if applicable, and overall.

**Presentation of continuous and qualitative variables:**

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

- number of participants with non-missing values (n)
- mean, standard deviation (StDev)
- median, 25th percentile - 75th percentile (Q1-Q3)
- minimum, maximum

Mean, median, Q1, Q3, Min, and Max will have the same precision as collected in SDTM datasets for non-derived data. Standard deviation will be presented with one digit more than the mean. Percentage and percent change from baseline will be reported using one decimal digit, if not specified otherwise. Derived data such as duration and "time since" variables (see Section 9.4) will be displayed with one decimal digit, unless stated otherwise.

If there are no missing values, the number of participants with missing values should be indicated by a 0.

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

For variables where a participant may have more than one category due to multiple responses per participant, the number of participants included in each category will be summarized as a percentage from all participants. Therefore, the total frequency across categories may not equal the total number of all participants in that analysis group.

**Scheduled and unscheduled visits**

Data collected at both scheduled and unscheduled visits will be included in the derivation of safety and efficacy endpoints.

Unscheduled visits will be included in the derivation of baseline or worst on-treatment values. Descriptive statistics by nominal visit or time point, e.g. for laboratory measurements, will include only data from scheduled visits

**Significance level:**

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

There will be no statistical tests performed. If confidence or credibility intervals are mentioned, the level will be 95% unless otherwise specified.

**Statistical software:**

All analyses will be performed using SAS® Software version 9.4 or higher.

## 9.1 Data Handling After Cut-off Date

By its nature, data after cut-off may be incomplete and subject to further change and will not be used for summary statistics, statistical analyses, listings or imputations.

Stop dates are not affected by this rule, e.g. a stop date of AEs, which starts prior to the cut-off, but stops after date of cut-off, will not be changed.

These rules will be applied to all analyses performed for the interim analysis for futility and main analysis. For the final analysis no cut-off date will be applied: the analysis will be performed only after all the data have been collected, fully cleaned and the database has been locked.

## 9.2 Definition of Baseline and Change from Baseline

In general, the last non-missing measurement prior to the first study drug administration will be used as the baseline measurement.

If the assessment time of any pre-dose baseline assessments (as planned per protocol) and/or the time of initial dosing are unknown, but they are known to have been performed on the same day, it will be assumed that it was performed prior to dosing. Unscheduled assessments may be used in the determination of baseline; however, if the time of either the assessment or initial dose is missing, the unscheduled assessment will be considered to have been obtained after study treatment administration.

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

Absolute and percent changes from baseline are defined as

absolute change = post baseline value – baseline value

percent change = 100 * (post baseline value – baseline value) / baseline value

## 9.3 Study Day / Study Treatment Day

Day 1 is the day of start of study treatment, the day before is Day -1 (no Day 0 is defined). Study day / Study treatment day is defined relative to Day 1.

## 9.4 Definition of Duration and 'time since' Variables

If not otherwise specified, duration will be calculated by the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of first study drug administration + 1).

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

## 9.5 Conversion Factors

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

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

If height is recorded in inches, height (cm) = height (in) × 2.54.

If weight is recorded in pounds, weight (kg) = weight (lb) ÷ 2.2046.

## 9.6 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 prior to or at the data cut-off 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
- Concomitant medication/procedures start and end dates
- Last known to be alive date collected on the 'Survival Follow-up' eCRF
- Tepotinib and cetuximab administration 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. This rule is to be applied to AE stop dates, too: if an AE started before the cut-off date and ended after the cut-off date, only the complete start date will be used in the derivation of the last date of contact.

## 9.7 Definition of On-treatment Period

The on-treatment period is defined as the time from the first dose of study treatment day to the last administration day of study treatment + 30 days, or the cut-off date or death or the start day of subsequent anti-cancer drug therapy - 1 day, whichever occurs first.

## 9.8 Imputation of Missing Data

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

Imputed dates will be used for the calculation of durations.

In all participant data listings, imputed or censored values will be presented, and imputed or censored information will be flagged.

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

Where tables are presented over different time points, the total of missing and non-missing observations at each time-point should reflect the population still in the trial at that time. This does not apply when imputations are made beyond trial withdrawal. For example, if a participant is still in the trial at the time-point but with missing data, they should be counted in the number of missing observations.

The following rules for imputation will be considered:

**Disease history**

Incomplete dates for disease history (e.g. initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease 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/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015. If the end date or resolution date indicates that the AE has stopped before start of treatment, this date will be used for imputation instead of start of treatment date.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after date of cut-off this date will be kept.

**Previous and concomitant medication/procedure**

For identification of previous or concomitant medications/procedures, no formal imputation will be performed on missing or incomplete dates. Rules presented in Table 2 and Table 3 will be used to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure.

**Table 2 Stopping rules for medication/procedure end dates**

| End date of medication/procedure | | | Stopping rule |
|---|---|---|---|
| **Day** | **Month** | **Year** | |
| UNK | UNK | UNK | After treatment start (ongoing) |
| UNK | UNK | < Treatment start (year) | Before treatment start |
| UNK | UNK | >= Treatment start (year) | After treatment start |
| UNK | < Treatment start (month and year) | | Before treatment start |
| UNK | >= Treatment start (month and year) | | After treatment start |
| < Treatment start (complete date) | | | Before treatment start |
| >= Treatment start (complete date) | | | After treatment start |

UNK = Unknown

**Table 3 Rules to define previous and/or concomitant medication**

| Start date of medication/procedure | | | Stopping rule (see Table 2) | Medication/procedure |
|---|---|---|---|---|
| Day | Month | Year | | |
| UNK | UNK | UNK | Before treatment start | Previous |
| UNK | UNK | UNK | After treatment start | Previous and concomitant |
| UNK | UNK | <= Treatment start (year) | Before treatment start | Previous |
| UNK | UNK | <= Treatment start (year) | After treatment start | Previous and concomitant |
| UNK | UNK | > Treatment start (year) and <= Treatment end + 30 days (year) | After treatment start | Concomitant |
| UNK | <= Treatment start (month and year) | | Before treatment start | Previous |
| UNK | <= Treatment start (month and year) | | After treatment start | Previous and concomitant |
| UNK | > Treatment start (month and year) and <= Treatment end + 30 days (month and year) | | After treatment start | Concomitant |
| <= Treatment start (date) | | | Before treatment start | Previous |
| <= Treatment start (date) | | | After treatment start | Previous and concomitant |
| > Treatment start (date) and <= Treatment end + 30 days (date) | | | After treatment start | Concomitant |

UNK = Unknown

## Dates of study treatment

Start date of study treatments:

- No imputation will be done.

End date of study treatments:

- In case the last date of study drug is missing or incomplete the date of last administration of study drug will be taken from the treatment termination eCRF pages.
- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date the participant should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date
- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the cut-off date) then imputed last dose date is:
  - 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

- Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)
- min (EOT date, death date), for all other case

**Death date**

In general, missing or partial death dates will not be imputed. However, for the purpose of survival analyses, partially missing death dates will be imputed as follows: if only the day is missing, the death date will be imputed to the maximum of the (non-imputed) day after the date of last contact (see Section 9.6) and the 15th day of the month.

**Tumor assessments**

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

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

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

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

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

**Dates of subsequent anti-cancer therapy**

Incomplete dates for start date of subsequent anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy related sensitivity analyses:

- If only day is missing, it will be imputed as the first day of the month unless it results in a date before the end date of study treatment. In that case, the incomplete anti-cancer therapy start date will be imputed as the end date of study treatment
- If both day and month are missing, the incomplete anti-cancer therapy start date will be imputed as the end date of study treatment if the subsequent therapy started on the same year as the end of study treatment; otherwise day and month will be imputed as the 1st of January.

Incomplete subsequent anti-cancer therapy stop dates will not be imputed.

## 9.9 Tumor Evaluation and Adjudication

Missing data from scheduled Tumor assessments not performed will not be imputed. Evaluable Tumor assessments are defined as those with overall response CR, PR, SD or PD. Data from non-evaluable (NE) Tumor assessments will be used in the derivation of endpoints in accordance with Eisenhauer et al., (2009).

In case IRC assessments are performed only the response assessments which are flagged as accepted after adjudication will be taken over to ADaM datasets and will be analyzed. In case of a missing adjudication flag for a response assessment and earliest image dates are equal, the assessment of reader 1 (the reader who completed baseline first) will be taken for analysis. Otherwise the assessment for the reviewer who reviewed the record with the earliest image date will be analyzed. Analyses of tumor sizes will be based only on assessments of the reader whose assessment was accepted at baseline.

# 10 Study Participants

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

## 10.1 Disposition of Participants and Discontinuations

The number and percentage of participants in each of the below disposition categories will be presented by cohort, by assigned dose level of tepotinib and overall. Percentages will be presented with respect to the number of participants in FAS/SAF analysis set.

Participant disposition will be summarized as follows:

- Number of participants in each analysis set (SCR, SAF, DLT, PKAS, IMAS)
- Number of participants who discontinued from the study prior to treatment overall and grouped by the main reason (e.g. the failed specific inclusion or exclusion criteria, withdrawal of consent)

The end of treatment status will be summarized by:

- Number of participants who received at least one dose of study treatment
- Number and percentage of participants who have permanently discontinued study treatment
- Number and percentage of participants with study treatment ongoing
- Number and percentage of participants who did not receive tepotinib
- Number and percentage of participants with tepotinib treatment ongoing

- Number and percentage of participants who permanently discontinued tepotinib treatment (overall and by primary reason)
- Number and percentage of participants who did not receive cetuximab
- Number and percentage of participants with cetuximab treatment ongoing
- Number and percentage of participants who permanently discontinued cetuximab treatment (overall and by primary reason)

The end of study status will be summarized by:

- Number and percentage of participants with any study treatment ongoing
- Number and percentage of participants off-treatment and in safety or survival follow-up
- Number and percentage of participants who discontinued the study (overall and by primary reason)

For each participant in the FAS/SAF analysis set, the first and last dosing date for each study component (including reason for treatment discontinuation) and study discontinuation date (including reason for study discontinuation) will be listed.

Additionally, the number of participants enrolled in each analysis population will be provided overall, by region, by country within region and by site. Results will be presented by cohort and by assigned dose level of tepotinib. This information will also be provided for each participant in the FAS/SAF analysis set in a listing.

Disposition of participants will be presented in a CONSORT Flow Diagram.

## 10.2 Protocol Deviations / Exclusion from Analysis Populations

### 10.2.1 Important Protocol Deviations

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

Important protocol deviations include, but are not limited to:

- Participants enrolled and dosed on the study who did not satisfy enrolment criteria
- Participants who are not compliant with treatment: overdose, dose modifications not as per protocol, incorrect dose, etc.
- Participants who receive a prohibited concomitant medication
- Failure to collect data necessary to interpret primary endpoints
- Failure to collect necessary key safety data
- Deviation from Good Clinical Practice (GCP)

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

All important protocol deviations are documented in SDTM datasets whether identified for all participants by either medical review processes or programming and confirmed prior to or at the Data Review Meeting at the latest.

The protocol deviations recorded in the Clinical Trial Management System (CTMS) may utilize different terminology. The table below displays how the terminology used in CTMS translates to the terminology used in the IAP, the SDTM and ADaM datasets, and ultimately the CSR:

| **CTMS** | **IAP** | **SDTM** | **ADaM** |
|---|---|---|---|
| Non-important | Non-important (only for protocol deviations related to COVID-19) | Only protocol deviations related to COVID-19 are included | Only protocol deviations related to COVID-19 are included |
| Important | Important | Flagged with PDEVXXX code | Flagged with PDEVXXX code |
| Relevant | Relevant for PK | Mapped to Important | Mapped to Important |

A full list of potential protocol deviations including definition and categorization is maintained by Covance in the "Study Specific Protocol Deviation List" attached to the Protocol Deviation Management Plan.

A frequency table (split by deviations from the inclusion and exclusion criteria as well as all other deviations) and a listing of important protocol deviations will be provided based on the SAF analysis set.

### 10.2.2 Reasons Leading to the Exclusion from an Analysis Population

Participants who have relevant protocol deviations or important events affecting PK will be excluded from PKAS.

## 11 Demographics and Other Baseline Characteristics

Demographic data and other baseline characteristics will be presented for the FAS/SAF analysis set using summary statistics for continuous variables and frequency statistics (i.e. counts and percentages) for categorical variables. Results will be presented as indicated in Section 10.

Listings showing demographic data and other baseline characteristics will be presented for the FAS.

## 11.1 Demographics

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

- Sex: male, female, undifferentiated
- Race: white, black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, not collected at this site, more than one race, other, missing
- Ethnicity:
  - Hispanic or Latino / Not Hispanic or Latino
- Age (years)
- Age categories:
  - < 65 years,
  - ≥ 65 years
  - 65-74,
  - 75-84,
  - ≥ 85 years
- Pooled Regions: Europe, North America
- Country (e.g.: Belgium, Czech Republic, France, Italy, Russia, Spain, United Kingdom, USA)

Specifications for computation:

- Age [years]:
  - Age = (01.JAN.YEAR informed consent date for screening – 01.JAN.YEAR of birthdate + 1) / 365.25.

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

- Site codes will be used for the determination of the participant's pooled region and country.
- Participants with more than one race will be summarized in the "more than one race" category.

## 11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using the most recent MedDRA version at time of database lock, preferred term as event category and system organ class (SOC). Each participant will be counted only once within each PT or SOC.

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

A listing will be provided with SOC term, PT term, toxicity grade and whether related to the study condition.

## 11.3 Disease History

Information on disease history is collected during the screening visit on the "Disease History" eCRF page. Data will be summarized and listed as follows:

- Site of Primary Tumor by International Classification of Diseases for Oncology (ICD-O) codes will be translated into text for presentation in outputs
- Time since initial cancer diagnosis (years) = (date of start of study treatment – date of initial cancer diagnosis + 1) / 365.25
- Time since documented locally advanced, inoperable or metastatic disease diagnosis (years) = (date of start of study treatment – date of documented locally advanced, inoperable or metastatic disease diagnosis + 1) / 365.25
- Tumor histopathologic / cytologic type: Adenocarcinoma / Mucinous adenocarcinoma/ Not differentiated cancer/ Neuroendocrine tumor/ Other
- Disease stage at initial diagnosis
- Disease stage at study entry
- TNM classification at initial diagnosis
- TNM classification at study entry

Incomplete dates for initial cancer diagnosis and documented locally advanced, inoperable or metastatic disease diagnosis will be handled as specified in Section 9.8.

## 11.4 Baseline Tumor Assessment

Information collected by the Investigator on the baseline tumor assessment collected at the screening visit on the "Tumor Assessment (according to RECIST 1.1)" eCRF pages and "Sum of Diameters (according to RECIST 1.1)" eCRF page will be presented. Summaries will be presented for the following:

- Target lesions (by investigator)
  - Number of target lesions
  - Sum of diameters (sum of longest diameters for non-nodal lesions, short axis for nodal lesions)
  - Type: Primary / Recurrence, Node, Metastasis
  - Site
- Non-target lesions (by investigator)
  - Number of participants with at least one non-target lesion
  - Number of non-target lesions
  - Type: Primary / Recurrence, Node, Metastasis
  - Site

Tumor information based on Investigator that is collected during the study will be listed.

## 11.5 Prior Anti-Cancer Therapy

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

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

- Prior anti-cancer drug therapy for locally advanced or metastatic disease (anti-EGFR as prior drug therapy)
  - Number of prior anti-cancer drug therapy lines: 1 / 2 / 3 / 4 / ≥ 5
  - Prior anti-cancer drug therapies
  - Prior anti-cancer drug combinations
  - Best response across all prior anti-cancer drug therapies: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (Non-CR/Non-PD) / Not Evaluable / Unknown
- Prior anti-cancer radiotherapy
  - Any prior anti-cancer radiotherapy: Yes / No
  - Number of prior anti-cancer radiotherapy regimen: 1 / 2 / 3 / ≥ 4
  - Best response across all prior anti-cancer radiotherapies: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (Non-CR/Non-PD) / Not Evaluable / Unknown.

- Prior anti-cancer surgery
  - Any prior anti-cancer surgery: Yes / No
  - Number of prior anti-cancer surgeries: 1 / 2 / 3 / ≥ 4
  - Prior anti-cancer surgeries outcome
  - Any prior surgery curative in intent: Yes / No
  - Best outcome across all prior anti-cancer surgeries: No residual tumor after resection (R0) / Tumor/metastases not resected completely with microscopic residual lesions (R1) / Tumor/metastases not resected completely with macroscopic residual lesions (R2) / Metastases not resected (NR), Other

The listings of prior anti-cancer treatments and procedures will also be provided as follows. These will include the participant identification number, and all the relevant collected data fields on the corresponding eCRF pages.

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

## 11.6 Other Baseline Characteristics

Information on other characteristics collected at baseline will be summarized and listed. Summary statistics will be presented for

- ECOG PS
- Height, weight, body surface area (BSA), and body mass index (BMI)

Specifications for computation:

- BSA [m²] = $\sqrt{\frac{height[cm] \times weight[kg]}{3600}}$
- BMI [kg/m²] = $\frac{\text{weight [kg]}}{\text{height[cm]}^2} \times 10000$
- In the formula above, values at baseline should be used for both weight and height.

ECOG PS, height, weight, BSA and BMI will be added to the listing presenting demographic data.

Other baseline characteristics such as vital signs, clinical laboratory evaluations and ECGs will be part of Section 15 (Safety Analyses).

# 12 Previous or Concomitant Medications/Procedures

The following analyses will be performed based on the SAF analysis set and presented as indicated in Section 9.

**Concomitant medications** are medications, other than study treatment, which are taken by participants any time during the on-treatment period, see Section 9.7.

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

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date. To derive these flags in case of missing or partial dates, see Section 9.8.

Concomitant and previous medications each will be summarized by number and percentage of participants from the "Concomitant Medications Details" eCRF page. ATC-2$^{nd}$ level and preferred term level will be tabulated as given from the WHO-DD dictionary most current version. If any previous or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted by ATC-2$^{nd}$ level and preferred term in alphabetical order. In case any specific medication does not have an ATC-2$^{nd}$ level coded term, it will be summarized under "UNCODED" ATC classification category. Each participant will only be counted once, even if he/she received the same medication at different times.

Any medication recorded on the "Concomitant Medications Details" eCRF page will be listed with an indication of whether the medication was previous, concomitant or both.

All **concurrent procedures**, which were undertaken during the on-treatment period, will be summarized according to the "Concomitant Procedures Details" eCRF page. Concurrent procedures will be classified using the most recent MedDRA version at the time of analysis.

A procedure will be considered concurrent if it started before the first dose of study treatment and was still ongoing when study treatment started or if it started after the first dose but during the on-treatment period. Number and percentage of participants with concurrent procedures will be presented by SOC and PT in descending frequency of the total column.

A listing with the relevant information about concurrent procedures will also be produced. A flag will be added to indicate whether the procedure is:

- Prior: the procedure started before the first dose of study treatment
- Concurrent: as defined above
- Post: the procedure started after the on-treatment period or during the on-treatment period but was still ongoing at the end of it.

A procedure could therefore be prior and concurrent as well as concurrent and post-treatment.

**Subsequent anti-cancer therapy**

The subsequent anti-cancer therapies are collected under the "Anti-Cancer Treatment After Discontinuation Details", "Radiotherapy after Discontinuation Details" and "Anti-Cancer Treatment After Discontinuation Details – Maximum Drugs" eCRF pages.

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

- Number of participants with subsequent anti-cancer treatment
- Subsequent anti-cancer drug therapy
  - Any subsequent anti-cancer drug therapy: Yes / No
  - Number of subsequent anti-cancer drug therapy lines: 1 / 2 / 3 / ≥ 4
  - Type of therapy
  - Intent of therapy: Metastatic/Locally advanced / Neoadjuvant / Adjuvant
  - Subsequent anti-cancer drugs
  - Best response across all subsequent anti-cancer drug therapies: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (Non-CR/Non-PD) / Not Evaluable / Unknown. For participants who received more than one anti-cancer drug therapy after treatment discontinuation, the best overall response among all anti-cancer drug therapies will be summarized.
- Subsequent radiotherapy
  - Any subsequent anti-cancer radiotherapy: Yes / No

The listings of subsequent anti-cancer treatments will also be provided as follows. These will include the participant identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of subsequent anti-cancer drug therapies
- Listing of subsequent anti-cancer radiotherapy

# 13 Study Treatment: Compliance and Exposure

All summaries and listings related to study treatment compliance and exposure will be based on the SAF analysis set.

All dosing calculations and summaries will be based on "Tepotinib Administration" and "Cetuximab Administration" CRF pages. The date of last drug administration will be taken from the "Tepotinib Termination" and "Cetuximab Termination" eCRF pages for those participants who have discontinued treatment by the cut-off date whereas for those participants who are still on-treatment, the last dosing date before or at the cut-off date will be used.

The date of last study drug administration will be defined as the last date in the "Tepotinib Administration" and "Cetuximab Administration" CRF pages, with dose > 0.

A dose of tepotinib will be regarded as being taken on a particular day if the actual dose of tepotinib taken is > 0 mg. Therefore, interruptions, compliance, and dose changes are not taken into account for the calculation of duration of therapy. The same would apply to cetuximab.

The following summary tables will be provided:

- Duration of therapy (weeks)
- Total number of 3-week cycles
- Cumulative actual dose (mg)
- Dose intensity (mg/3-week cycle)
- Relative dose intensity (%)
- Number of cetuximab infusions

**Duration of therapy**

Duration of therapy is defined as

$$\text{Duration of therapy (in weeks)} = \left(\frac{\text{Date of last dosing day - Date of first dosing day + D}}{7}\right)$$

where D = 1 for tepotinib and D = 7 for cetuximab.

The total number of 3-week cycles is defined as the duration of therapy (in weeks)/3.

For categorical summary, use floor (duration of therapy) i.e. round the value to completed cycles. For summary statistics take the duration value as such.

**Cumulative actual dose of tepotinib**

The cumulative actual dose (mg) per participant in a time period is the sum of the total doses that the participant received within that period (i.e. total dose administered (mg)).

**Dose intensity and relative dose intensity of tepotinib**

The dose intensity and the relative dose intensity will be calculated for a 3-week cycle. The dose intensity (mg/3-week cycle) per participant) is defined as:

$$\text{Actual dose intensity (mg/3-week cycle)} = \left(\frac{\text{Cumulative actual dose (mg)}}{\text{Total number of 3-week cycles}}\right)$$

Relative dose intensity per participant is defined as:

$$\text{Relative dose intensity (\%)} = 100 \times \left(\frac{\text{Actual dose intensity}}{\text{Intended dose intensity by 3-week cycle}}\right)$$

where intended dose intensity (mg/3-week cycle) = RP2D mg * 21 days for tepotinib.

A dose of cetuximab is regarded to be administered, if the actual dose of cetuximab received is > 0, or the duration of the infusion is > 0.

For Cycle X, actual cycle start date for each participant is

- the earliest start date of dosing in the Cycle X day 1 visit eCRF exposure page, if the participant received study treatment on that visit (i.e., any study drug with dose > 0 at that visit)
- the first day of assessments in the Cycle X day 1 visit, if the participant did not receive study treatment on that visit (i.e., all study drugs had dose = 0 at that visit). Use start date in the exposure page if available; if start date is not available then use date of collection of vital signs (assuming vital signs are the first assessment of the cycle on Cycle X day 1 visit).

Actual cycle end date for each participant is,

- for all cycles X except the last cycle, actual cycle end date = actual cycle (X+1) start date – 1 day;
- for the last cycle, actual cycle end date = actual cycle start date + intended cycle duration (21 days) – 1 day

**Cumulative actual dose of cetuximab**

The cumulative dose (mg/m²) from 1st infusion 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) / recalculated BSA ($m^2$)).

**Dose intensity and relative dose intensity of cetuximab**

Actual dose intensity (mg/m²/3-week cycle) per participant is defined as:

$$\text{Actual dose intensity} = \left(\frac{\text{Cumulative dose from 1st infusion}}{\text{Total number of 3-week cycles}}\right)$$

Relative dose intensity per participant is defined as:

$$\text{Relative dose intensity (\%)} = 100 \times \left(\frac{\text{Actual dose intensity}}{\text{Intended dose intensity by 3-week cycle}}\right)$$

where intended dose intensity by 3-week cycle (mg/m$^2$/3-week cycle) per participant is defined as

- for the first cycle:
  - 400 mg/m$^2$ + 2 x 250 mg/m$^2$ per 3-week cycle, if loading dose is needed
  - 3 x 250 mg/m$^2$ per 3-week cycle, if loading dose is not needed
- for the subsequent cycles: 3 x 250 mg/m$^2$ per 3-week cycle

**Dose reductions**

If the 500 mg dose for tepotinib will be the selected RP2D, participants may have a dose reduction to 250 mg, which is also the minimum possible dose in this study. If 250 mg is the RP2D for tepotinib, then no further reduction will be possible.

For cetuximab the loading dose is 400 mg/m$^2$ and subsequent weekly doses are 250 mg/m$^2$ if the loading dose is required or the weekly dose is 250 mg/m$^2$ if the loading dose is not required. The weekly dose can be reduced to 200 mg/m$^2$ or 150 mg/m$^2$ for safety reasons if necessary.

The number of participants with and without any dose reduction will be summarized. In case the selected RP2D is 250 mg, the tepotinib sections will contain "NA" (Not Applicable).

Number of participants with any dose adjustment due to Adverse Event/Other will be provided.

**Dose interruptions and therapy delays**

For tepotinib any days within the treatment period where the participants did not take any tepotinib will be counted as dose interruptions. Number of participants with any tepotinib interruptions will be presented.

Dose delays are applicable for cetuximab only. It will be derived by administration as the number of days between two successive administrations greater than 7 and will be presented as follows:

- Number of participants with delayed infusions, and maximum length of delay (no delay, 3-8 days, 9-15 days, ≥ 16 days) – worst case

Treatment administration of tepotinib and cetuximab by time point will be listed.

# 14 Efficacy Analyses

The following analyses will be performed based on the FAS and will be presented by cohort and assigned dose level of tepotinib, except when otherwise stated.

## 14.1 Primary Endpoint (Overall Study): Objective Response

### 14.1.1 Derivation and analysis

Best Overall response (BOR) will be assessed based on reported overall responses at different evaluation time points from the study treatment start date until documented disease progression in accordance to RECIST v1.1 by investigator, taking requirements for confirmation into account as detailed below.

Only tumor assessments performed before the start of any subsequent anti-cancer therapies 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. The date of the overall response assessment is the earliest date for imaging of target, non-target and new lesions of images taken at that response assessment.

**BOR Based on Confirmed Responses:**

- Complete Response (CR) = at least two determinations of CR at least 4 weeks apart (with no PD in between)
- Partial Response (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
- Stable Disease (SD) = at least one SD assessment (or better) ≥ 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) ≥ 6 weeks after start date (and not qualifying for CR or PR).
- Progressive Disease (PD) = PD ≤ 12 weeks after start date of study treatment (and not qualifying for CR, PR, non-CR/non-PD or SD).
- Not Evaluable (NE): all other cases.

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

Participants are defined as having an Objective Response (OR) if they achieved either a BOR of confirmed CR or confirmed PR according to RECIST v1.1 as assessed by the investigator, from first administration of study treatment to first observation of PD.

Participants who do not have an on-treatment radiographic tumor assessment due to early progression, who receive anti-tumor treatments other than the study treatments prior to reaching confirmed CR or

PR, or who die, progress, or drop out for any reason prior to reaching confirmed CR or PR will be counted as non-responders in the assessment of OR. Each participant will have an objective response status (0: 'no OR'; 1: 'OR'). OR rate (ORR) is the proportion of participants with OR in the analysis set. No formal statistical hypotheses will be tested.

The number and percentage of participants with BOR of confirmed CR, confirmed PR, SD, PD, and NE will be tabulated.

The confirmed ORR by cohort and assigned dose level of tepotinib will be presented along with the two-sided 95% CI using the Clopper-Pearson method (1934) (exact CI for a binomial proportion as computed by default by the SAS FREQ procedure using the EXACT option).

A spider plot will show the participant profiles of the sum of target lesion diameters (sum of longest diameters for non-nodal lesions, short axis for nodal lesions) over time (presenting all participants on the same graph). In addition, a waterfall plot will show the change in sum of target lesion diameters between baseline and the best post-baseline assessment for each participant.

Time to and duration of response by investigator assessment for every participant will be plotted using a swimmer plot. Color coded symbols will be used to show the time of the following events: CR, PR, PD, death, ongoing response and end of treatment.

**Estimand Attributes**

**Endpoint:**

- OR according to RECIST 1.1 assessed by Investigator prior to further anti-cancer therapy and progression

**Population:**

- Participants with *RAS*/*BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) having acquired resistance to anti-EGFR antibody targeting therapy due to *MET* amplification

**Treatment:**

- Tepotinib combined with cetuximab

**Intercurrent Event Strategy:**

- Discontinuation of treatment (treatment-policy strategy, i.e. regardless of the intercurrent event)
- Start of subsequent anti-cancer therapy (while not treated with subsequent anti-cancer therapy strategy, i.e. assessments up to the intercurrent event)
- Progression according to RECIST 1.1 (while not progressed strategy, i.e. assessments up to the intercurrent event)

**Population Level Summary:**

- Rate

### 14.1.2 Sensitivity Analyses

A sensitivity analysis will be conducted in which the start of any other anti-cancer treatment or procedure prior to study discontinuation will be considered as PD, and any subsequent tumor assessments will not be considered in the objective response assessment. If only partial dates are known for the start of other anti-cancer treatment or procedures, the imputation rules described in Section 9.8 should be followed.

### 14.1.3 Futility Analysis

Best Overall Response (BOR) as described above will be reported for the first 12 participants, in Cohort A. If there are less than 2 responders (confirmed CR or PR) the enrollment of 2nd line participants for the study might be stopped for futility.

### 14.1.4 Subgroup Analyses

Subgroup analyses will be performed on the primary endpoint by cohort and assigned dose level of tepotinib for all the baseline subgroup levels defined in Section 8.2. All the subgroup analyses are exploratory and no adjustment for multiplicity will be performed. In case of low number of participants within a subgroup level (< 5 participants), levels will be pooled when meaningful.

For each subgroup, the BOR, the number of participants achieving objective response, and the ORR along with the two-sided exact Clopper-Pearson 95% CIs will be presented.

In addition to the presentation in summary tables, forest plots will be created to graphically present ORRs and corresponding 95% CIs.

## 14.2 Secondary Endpoints

### 14.2.1 Duration of Response

Duration of Response (DoR) as assessed by Investigator will only be evaluated in participants with objective response (as defined in Section 14.1.1).

DoR is the time from when the CR/PR (whichever is first) criteria are first met until PD or death due to any cause within the period of 2 scheduled tumor assessments (84 or 168 days) after the last tumor assessment, whichever occurs first (see Eisenhauer EA, et al 2009) (i.e. date of PD/death - date of last evaluable tumor assessment ≤ 84 or 168).

DoR data will be censored on the date of the last evaluable tumor assessment for participants who do not have an event (PD or death) or for participants with an event after the period of 2 scheduled tumor assessment (more than 84 or 168 days) after the last evaluable tumor assessment (i.e. date of PD/death

- date of last evaluable tumor assessment > 84 or 168). Participants who do not have a tumor assessment after objective response will be censored at the date CR/PR criteria are first met.

The last evaluable tumor assessment is defined as the last tumor assessment result that is not "NE".

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics for duration of response: median and corresponding two-sided 95% confidence interval (CI), Q1 and Q3, minimum and maximum. DoR rate estimates at 3, 6, 9, 12, 15, 18 months and for every 3 months thereafter as applicable including the corresponding two-sided 95% CIs will also be reported. The CI for the median will be calculated according to Brookmeyer and Crowley (1982) and CIs for the survival function estimates at the above defined time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980) (conftype=loglog default option in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula. Kaplan-Meier plots will also be presented.

Time to and duration of response as assessed by Investigator for every participant will be plotted using a swimmer plot. Symbols color coded will be used to show the time of the following events: complete response, partial response, progressive disease, death, ongoing response and end of treatment.

**Estimand Attributes**

**Endpoint:**

- DoR according to RECIST 1.1 as assessed by Investigator, measured by time from first documentation of objective response to PD or death, occurring within 2 scheduled tumor assessments (84 or 164 days, respectively) after last evaluable assessment or first dose

**Population:**

- Participants with *RAS*/*BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) having acquired resistance to anti-EGFR antibody targeting therapy due to *MET* amplification

**Treatment:**

- Tepotinib combined with cetuximab

**Intercurrent Event Strategy:**

- Discontinuation of treatment (treatment-policy strategy, i.e. regardless of the intercurrent event)
- Start of subsequent anti-cancer treatment (treatment-policy strategy, i.e. regardless of the intercurrent event)
- Death within two scheduled tumor assessments after last evaluable assessment will be considered as event of interest (composite strategy)

**Population Level Summary:**

- Kaplan-Meier estimates

**Follow-up for duration of response**

In order to assess the follow-up for duration of response, Kaplan-Meier estimates will be calculated using the censoring rules with reverse censoring indicator.

Kaplan-Meier estimates (product-limit estimates) will be presented in the same way as in the analysis described above for duration of response.

The following information will also be presented:

- Number of participants with Objective Response (confirmed CR/PR)
- Number of responders (confirmed CR/PR) with duration of response: ≥ 6 months / ≥ 9 months / ≥ 12 months
- Number of responders (confirmed CR/PR):
  - with ≥ 6 months follow-up from onset of response (CR, PR or SD) or event (PD or death) or who discontinued treatment < 6 months after onset of response
  - Ongoing response with < 6 months duration, on treatment

### 14.2.2 Progression Free Survival

Progression Free Survival (PFS) time as assessed by Investigator is defined as the time (in months) from first administration of study intervention to the date of the first documentation of PD or death due to any cause, whichever occurs first if only the event happened within the period of 2 scheduled assessments (84 or 168 days) after the last tumor assessment (i.e. time between date of PD/death - date of last evaluable tumor assessment ≤ 84 or 168 days). The tumor response will be determined according to RECIST 1.1. and assessed by the investigator.

PFS data will be censored on the date of the last evaluable tumor assessment for participants who do not have an event (PD or death) or for participants with an event after the period of 2 scheduled tumor assessments (84 or 168 days) after the last tumor assessment (i.e. date of PD/death - date of last evaluable tumor assessment > 84 or >168 days).

The last evaluable tumor assessment is defined as the last tumor assessment result that is not “NE”.

Participants who do not have a baseline tumor assessment or who do not have any post baseline tumor assessments will be censored at the date of the start of study intervention.

Participants who do not have an evaluable post-baseline tumor assessment will be censored at the date of the start of study treatment unless death occurred within the period of 2 scheduled tumor assessments (84 or 168 days, respectively) after the first dose of study treatment in which case the death will be considered an event.

The censoring and event date options to be considered for the PFS are presented in Table 5.

**Table 4. Date of event / censoring definition for PFS analysis**

| Status | | Censoring | Date of event / censoring |
|---|---|---|---|
| Progressed or died | Within the period of 2 scheduled tumor assessment (84 or 168 days, respectively) after last response assessment of CR, PR or SD or start of treatment | Event | Minimum (Date of PD, Date of death) |
| | Otherwise | Censored | Date of last tumor assessment with outcome CR, PR or SD or date of start of treatment, whatever is later |
| Neither progressed nor died | | Censored | Date of last tumor assessment with outcome CR, PR or SD or date of start of treatment, whatever is later |

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease.

Kaplan-Meier product-limit estimates will be presented together with a summary of associated statistics for PFS: median and corresponding two-sided 95% confidence interval (CI), Q1 and Q3, minimum and maximum. Progression-free rate estimates at 3, 6, 9, 12, 15, 18 months and for every 3 months thereafter as applicable including the corresponding two-sided 95% CIs will also be reported. The CI for the median will be calculated according to Brookmeyer and Crowley (1982) and CIs for the survival function estimates at the above defined time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980) (conftype=loglog default option in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula. Kaplan-Meier plots will also be presented.

**Estimand Attributes**

**Endpoint:**

- Progression-free survival time, defined as the time from first dose until PD according to RECIST 1.1 or death events occurring within two scheduled tumor assessments after last evaluable assessment or first dose

**Population:**

- Participants with *RAS*/*BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) having acquired resistance to anti-EGFR antibody targeting therapy due to *MET* amplification

**Treatment:**

- Tepotinib combined with cetuximab

**Intercurrent Event Strategy:**

- Discontinuation of treatment (treatment-policy strategy, i.e. regardless of the intercurrent event)
- Start of subsequent anti-cancer treatment (treatment-policy strategy, i.e. regardless of the intercurrent event)

- Death within two scheduled tumor assessments after last evaluable assessment will be considered as event of interest (composite strategy)

**Population Level Summary:**

- Kaplan-Meier estimates

**Follow-Up Duration of PFS**

In order to assess the follow-up duration of PFS, Kaplan-Meier estimates will be calculated using the censoring rules with the reverse censoring indicator.

Kaplan-Meier estimates (product-limit estimates) will be presented in the same way as in the analysis described above for PFS.

### 14.2.3 Overall Survival

Overall survival (OS) time is defined as the time (in months) from the first administration of study treatment to the date of death.

For participants not known to be deceased at time of analysis or who died after the cut-off date, OS time will be censored at the date of last contact before data cut-off date as defined in Section 9.66.

The Kaplan-Meier based analysis described in Section 14.2.2 for the derivation of progression-free related estimates will be repeated for the survival related estimates.

The censoring and event status with respect to OS will be summarized

**Estimand Attributes**
**Endpoint:**

- OS as measured by time from first dose to death

**Population:**

- Participants with *RAS*/*BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) having acquired resistance to anti-EGFR antibody targeting therapy due to *MET* amplification

**Treatment:**

- Tepotinib combined with cetuximab

**Intercurrent Event Strategy:**

- Discontinuation of treatment (treatment-policy strategy, i.e. regardless of the intercurrent event)
- Start of subsequent anti-cancer treatment (treatment-policy strategy, i.e. regardless of the intercurrent event)

**Population Level Summary:**

- Kaplan-Meier estimates

**Follow-Up Duration of OS**

In order to assess the follow-up duration of OS, Kaplan Meier estimates will be calculated reversing the OS censoring and event indicators.

Kaplan-Meier estimates (product-limit estimates) will be presented in the same way as in the analysis described above for OS.

### 14.2.4 Immunogenicity

Immunogenicity of cetuximab will be measured by ADA assays at Baseline on Day 1 Cycle 1 and End of Treatment Visit.

Immunogenicity of cetuximab will be tabulated by cohort and dose level, if applicable, based on Immunogenicity Analysis Set. The immunogenicity status of each study participant will be evaluated according to the criteria described in Table 5.

**Table 5 Immunogenicity classification**

| ADA result at Baseline | ADA result at EOT | Classification |
|---|---|---|
| Negative | Negative | Treatment-emergent negative |
| Negative | Positive | Treatment-emergent positive |
| Positive | Negative, or positive with titer lower or equal to baseline | Treatment-emergent negative |
| Positive | Positive with titer higher than baseline | Treatment-emergent positive |
| Missing | Negative or positive | Not evaluable |
| Negative or positive | Missing | Not evaluable |
| Missing | Missing | Not evaluable |

Immunogenicity of cetuximab will be listed.

### 14.2.5 Subgroup Analyses

Subgroup analyses for secondary endpoints of DoR, PFS and OS will be performed by cohort and assigned dose level of tepotinib for all the baseline subgroup levels identified in Section 8.2.

The Kaplan-Meier based analysis described in Section 14.2.2 will be repeated for all the baseline subgroups. The same rules described in the first paragraph of Section 14.2.2 will apply.

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## 15 Safety Analyses

The analysis of the primary safety endpoint will be performed on the DLT analysis set whereas the analyses of the secondary safety endpoints will be performed on the SAF analysis set.

In case the RP2D for tepotinib is 250 mg and there are participants who started on the 500 mg dose, a selection of the safety tables may be repeated on these participants, otherwise their data will only be listed.

The safety analyses will be done purely descriptively.

### 15.1 Primary Endpoint (Safety Run-in): Occurrence of DLTs

The number and percentage of participants in the DLT analysis set with no DLT, 1 DLT or 2 or more DLTs observed during the DLT observation period will be tabulated together with the respective SOCs and PTs as well as the number of participants with any TEAE during cycle 1.

All DLT relevant data will also be listed.

DLT evaluation by the Investigator as well as by the SMC will be available for the analyses. In the "Adverse Event Details" eCRF page, the question "Is this adverse event a dose limiting toxicity" will

be used to identify the DLTs within 21 days after start of study treatment (DLT observation period) by Investigator assessment. SMC decisions will be implemented programmatically into SDTM dataset based on SMC feedback received.

## 15.2 Secondary Endpoints

### 15.2.1 Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA; latest version at the time of database lock for each analysis will be used and be specified in outputs). Severity of AEs will be graded using the NCI-CTCAE (Version 5.0) toxicity grades.

Relationship with the study treatment components are collected in the "Adverse Events Details" eCRF page. Adverse Events can be related to tepotinib, cetuximab or both. In case the relationship information is missing for a study treatment component, the AE will be considered as related to that component.

Incomplete AE-related dates will be handled as specified in Section 9.8.

Treatment emergent adverse events (TEAE) are those events that occurred during on-treatment period, having been absent prior to treatment or worsened relative to the pre-treatment state and with onset dates occurring within the first dosing day of study intervention until 30 days after the last dose of study intervention.

For the Adverse Event that started before the first administration of study treatment, the latest toxicity grade before first dose will be considered as the baseline grade and used to assess whether the AE worsens during the on-treatment period.

Pre-existing conditions continuing on-treatment with grade equal or lower than the baseline grade will not be considered as TEAEs.

All analyses described in Section 15.2.2 and 15.2.3 will be based on TEAEs if not otherwise specified. The AE listings will include all AEs (whether treatment emergent or not). A flag will be added to indicate if the AE is treatment emergent (i.e. started or worsened between the date of first dose of the study treatment and the date of last dose + 30 days).

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with the TEAE in the category of interest and sorted by primary System Organ Class (SOC) and Preferred Term (PT) in alphabetic order.

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

### 15.2.2 All Adverse Events

Adverse Event information is collected on the "Adverse Events Details" eCRF page.

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 5.0) per participant, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC).

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.

Incomplete AE-related dates will be handled as specified in Section 9.8.

The overall summary of AEs table will include the frequency (number and percentage) of participants within the following categories:

- TEAEs
- Study treatment related TEAEs (any study treatment and by study treatment components)
- Serious TEAEs
- Study treatment related serious TEAEs (any study treatment and by study treatment components)
- TEAEs with NCI-CTCAE Grade ≥ 3 and ≥ 4
- Study treatment related TEAEs with NCI-CTCAE Grade ≥ 3 and ≥ 4 (any study treatment and by study treatment components)
- TEAEs leading to death
- Study treatment related TEAEs leading to death (any study treatment and by study treatment components)
- Adverse Events of Special Interest (AESIs)

Adverse events of special interest are defined as events suggestive of drug-induced liver injury including hepatic / liver failure and hepatitis (non-infectious). The question "Is this an adverse event of special interest" present on the "Adverse Event Details" eCRF page will be used to identify these AEs.

In addition, the following tables summarizing the frequency of participants with TEAEs by SOC and PT will be produced:

- TEAEs
- Study treatment related TEAEs (any study treatment and by study treatment components)
- Serious TEAEs
- Non-serious TEAEs applying a frequency threshold of 5%

- Study treatment related serious TEAEs (any study treatment and by study treatment components)
- TEAEs by worst NCI-CTCAE Grade (Any, ≥ 3, ≥ 4 and 5)
- Study treatment related TEAEs by worst NCI-CTCAE Grade (Any, ≥ 3, ≥ 4) (any study treatment and by study treatment components)
- TEAEs leading to death
- Study treatment related TEAEs leading to death (any study treatment and by study treatment components)
- Adverse Events of Special Interest (AESIs)

Participant listings of AEs details collected on the "Adverse Events Details" eCRF page will also be provided for each of the following:

- AEs
- AESIs
- Serious TEAEs

TEAEs frequency and worst grade for TEAEs occurring in >= 10% participants will be plotted by cohort.

### 15.2.3 Adverse Events Leading to Discontinuation / Dose Reduction of Study Treatment

The frequency (number and percentage) of participants with each of the following will be presented in a summary table:

- TEAEs leading to temporary discontinuation of study treatment (any study treatment and by study treatment components)
- Study treatment related TEAEs leading to temporary discontinuation of study treatment (any study treatment and by study treatment components)
- TEAEs leading to permanent discontinuation of study treatment (any study treatment and by study treatment components)
- Study treatment related TEAEs leading to permanent discontinuation of study treatment (any study treatment and by study treatment components)
- TEAEs leading to dose reduction of study treatment (any study treatment and by study treatment components)
- Study treatment related TEAEs leading to dose reduction of study treatment, (any study treatment and by study treatment components)

In addition, tables summarizing the frequency of participants with AEs, presented by SOC and PT, in the above categories will be prepared. Tables summarizing TEAEs related to study treatment will be created to summarize TEAEs related to any study treatment and will be repeated to summarize TEAEs related to specific study treatment components (i.e. tepotinib and cetuximab).

Actions that can be taken by the Investigator to address an Adverse Event are collected by sections "Action(s) taken with Tepotinib" and "Action(s) taken with cetuximab" on the "Adverse Events Details" eCRF page. It is possible that a TEAE leads to more than one action: for example, a drug interruption followed by drug withdrawn. In this case the TEAE will be counted among the TEAEs leading to temporary discontinuation as well as among the TEAEs leading to permanent discontinuation.

Participant listings showing the relevant information will also be provided:

- AEs leading to permanent discontinuation of study treatment
- AEs leading to temporary discontinuation of study treatment

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

### 15.3.1 Deaths

All deaths, deaths within 30 days after last dose of study treatment and deaths beyond this period up to 90 days follow-up and reasons for them will be tabulated based on information from the "Death" eCRF page.

- Number of deaths overall and by primary reason
- Number of deaths within 30 days after last dose of study treatment overall and by primary reason
- Number of deaths within 90 days after last dose of study treatment overall and by primary reason

Primary reasons for death can be:

- Progressive disease and/or disease related condition
- Event unrelated to tepotinib and cetuximab
- Event related to tepotinib
- Event related to cetuximab
- Event related to tepotinib and cetuximab
- Unknown
- Missing

In addition, date and cause of death will be provided in individual participant data listing together with selected dosing information (date of first / last administration, dose and number of doses separately for tepotinib and cetuximab). This listing will also include:

- AEs with fatal outcome (list preferred terms of AEs with outcome = fatal)
- Flag for death within 30 days of last study treatment
- Flag for death within 90 days of last study treatment

Note: for the definition of "study treatment", "first" and "end"/last date of study treatment, please see Section 9.

### 15.3.2 Serious Adverse Events

The frequency tables as listed in Section 15.2.2 will be prepared for serious adverse events (SAEs).

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

### 15.3.3 Other Significant Adverse Events

Please refer to Section 15.2.2 for the analysis of AEs of special interest.

## 15.4 Clinical Laboratory Evaluation

Laboratory assessments such as hematology and coagulation, biochemistry, urinalysis and other screening tests (e.g.: pregnancy tests) will be performed by local laboratories.

Laboratory results will be classified according to the NCI-CTCAE criteria version 5.0. Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

The last measurement before study treatment first dose (including unscheduled measurements) will serve as the baseline measurement. For further details about baseline and change from baseline, please refer to Section 9.2.

Values below the detection limit will be imputed by half of the detection limit.

In case just a text value with an "> x" is reported it will be analyzed as +1 significant digit, e.g. "> 7.2 mmol" will be analyzed as 7.3.

Quantitative data will be summarized using descriptive statistics (n, mean, StDev, median, Q1, Q3, minimum, and maximum) of actual values and absolute changes from baseline to each scheduled visit over time. Scheduled visits performed during the safety run-in are to be presented, too.

Qualitative data based on reference ranges will be described according to the categories Low, Normal, and High (Hematology, Biochemistry and Coagulation). For qualitative data of urinalysis measurements, the raw classifications Normal, Trace/+, ++, +++, ++++ will be used instead. Results from the urinalysis microscopic examination (Erythrocytes, Leukocytes, Epithelial cells, Bacteria, Crystals and Casts) will only be listed.

Abnormalities classified according to NCI-CTCAE toxicity grading version 5.0 will be described using the worst on-treatment grade. Measurements from both scheduled and unscheduled visits should be considered for the worst on-treatment grade derivation; also measurements performed during the safety run-in are to be taken into account. For those parameters which are graded with two directions of 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 NCI-CTC 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 ≥ 800/$mm^3$
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 1500/$mm^3$

For **calcium**, NCI-CTC 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])

where the albumin values should be taken from the same sample, analyzed in the same laboratory as calcium.

**Liver function tests**: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

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

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

Concurrent measurements are those occurring on the same date.

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

Liver function elevation and possible Hy's Law cases will be summarized using frequency and percentage. An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment groups, 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 participants with a post-baseline TBILI ≥ 2 × ULN, ALT ≥ 3 × ULN or AST ≥ 3 × ULN will be provided.

Estimated glomerular filtration rate (GFR [mL/min/1.73 $m^2$]) will be derived using 4-component Modification of Diet in Renal Disease (MDRD) formula:

- GFR [mL/min/1.73 $m^2$] = 175 × serum creatinine (mg/dL)$^{-1.154}$ × age$^{-0.203}$ × 1.212 [if African American] × 0.742 [if female]

In case only Urea or only Blood Urea Nitrogen (BUN) is collected for a participant at a specific visit conversion factors will be programmatically applied. Urea results will only be presented in listings.

Urea will be calculated using BUN, as follows:

- if BUN is expressed in mmol/L then
  - urea [mmol/L] = BUN [mmol/L]

and needs to be converted to urea [mg/dL] using the following formula:

  - urea [mg/dL] = BUN [mmol/L] × 0.357
- if BUN is expressed in mg/dL then:
  - urea [mg/dL] = BUN [mg/dL] × 2.1428

**Parameters with NCI-CTC grades available**:

Laboratory toxicities will be tabulated (count and percentage) for each gradable parameter by the worst on-treatment NCI-CTC grade. For selected parameters with the on-treatment grading depending on baseline grading (as indicated in Appendix 1), the worst on-treatment grade will be tabulated by the status at baseline (normal or abnormal). Shifts from baseline to worst NCI-CTC grade during the on-treatment period will also be tabulated. The denominator to calculate percentages for each laboratory parameter is the number of participants in each analyzed group. Participants without baseline or on-treatment post-baseline results for a given parameter will be presented in the "Missing" category and will contribute to the denominator.

Please see Appendix 1 for a list of the NCI-CTC -gradable parameters.

**Parameters with NCI-CTC grades not available**:

Laboratory abnormalities will be tabulated (count and percentage) for each non-gradable parameter by the worst on-treatment abnormality. Shift tables from baseline to each time point as well as to worst abnormality during the on-treatment period will also be tabulated. For each parameter, the shift to the maximum post-baseline as well as the minimum post-baseline value will be presented. The denominator to calculate percentages for each laboratory parameter is the number of participants in each analyzed group. Participants without baseline or post-baseline results for a given parameter will be presented in the "Missing" category and will contribute to the denominator.

Following figures will be provided for each above-mentioned test:

- Boxplots of the laboratory values by time point.
- Boxplots of the change from baseline by time point.

Boxplots for laboratory parameters where toxicity grades are defined based on the ratio of the parameter values and the upper limit of normal (ULN) will not be displayed using the unit of measurement but instead using the ratio of the measured value over ULN. This comprises ALP, ALT, AST, bilirubin, creatinine.

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each participant. Laboratory values that are outside the normal range will be flagged in the data listings, along with corresponding normal ranges and CTCAE grades.

Results from pregnancy tests, both serum and urine, collected on the "Pregnancy Test" eCRF page will be listed.

## 15.5 Vital Signs

The maximum change (increase and decrease) in each vital sign measurement from baseline (where baseline is defined in Section 9.2) across on-treatment scheduled and unscheduled visits will be derived for each participant as shown below. Measurements performed during the safety run-in are to be taken into account, too. Refer to Section 9.7 for the definition of on-treatment.

| **Baseline category** | **Maximum change from baseline categories** |
|---|---|
| Body temperature increase<br>< 37 °C, 37 - < 38 °C, 38 - < 39 °C, 39 - < 40 °C, >= 40 °C | < 1 °C, 1 -< 2 °C, 2 -< 3 °C, ≥ 3 °C |
| Pulse increase from baseline < 100 bpm; ≥ 100 bpm | ≤ 20 bpm, > 20 – 40 bpm, > 40 bpm |
| Pulse decrease from baseline < 100 bpm; ≥ 100 bpm | ≤ 20 bpm, > 20 – 40 bpm, > 40 bpm |
| SBP increase from baseline < 140 mmHg; ≥ 140 mmHg | ≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg |
| SBP decrease from baseline < 140 mmHg; ≥ 140 mmHg | ≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg |
| DBP increase from baseline < 90 mmHg; ≥ 90 mmHg | ≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg |
| DBP decrease from baseline < 90 mmHg; ≥ 90 mmHg | ≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg |
| Respiration rate increase from baseline < 20 bpm; ≥ 20 bpm | ≤ 5 bpm, > 5 – 10 bpm, > 10 bpm |
| Respiration rate decrease from baseline < 20 bpm; ≥ 20 bpm | ≤ 5 bpm, > 5 – 10 bpm, > 10 bpm |

The number and percentage of participants in each category will be presented as a shift table showing baseline category versus the maximum change. The denominator to calculate percentages for each vital sign parameter is the number of participants in each analyzed group. Participants without baseline or post-baseline results for a given parameter will be presented in the "Missing" category and will contribute to the denominator.

For body weight, the number and percentage of participants with a maximum on-treatment percentage change from baseline increase and decrease will be presented. Categories will be: < 10%, ≥ 10% and missing. Those subjects with no baseline and/or post-baseline measurement will be presented in the "Missing" category.

A participant data listing will present the baseline value and maximum changes (increases and decreases) in each vital sign measurement. A listing presenting all vital sign measurements will also be produced.

## 15.6 Other Safety or Tolerability Evaluations

### 15.6.1 ECOG Performance Status

ECOG Performance Status information is collected on the "ECOG Performance Status" eCRF page.

ECOG Performance Status will be summarized using shift tables showing baseline versus minimum and maximum on-treatment values. Participants without baseline or on-treatment post-baseline results will be presented in the "Missing" category and will contribute to the denominator. Refer to Section 9.7 for the definition of on-treatment.

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

### 15.6.2 Electrocardiogram (ECG)

Triplicate 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTcF intervals. Electrocardiogram (ECG) results will be read locally, and all the three results will be reported in EDC.

For each of the ECG parameters (HR, and QT, QTcF, QRS, PR intervals), descriptive statistics for the average at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point will be presented. Scheduled visits performed during the safety run-in are to be presented, too.

The ECG assessment [Normal, Abnormal (not clinically significant), Abnormal (clinically significant)] will be presented as a shift table showing baseline versus the worst on-treatment result. For the derivation of the worst on-treatment value, measurements collected during the safety run-in should be considered too. Refer to Section 9.7 for the definition of on-treatment.

The change in QT interval corrected for the heart rate by the Fridericia's formula (i.e. QTcF) between baseline and the worst (longest) on-treatment result will be summarized in shift tables as follows:

Categorical shift from baseline to worst on-treatment value for the QTcF:

| Parameter | Baseline category | Worst on-treatment value |
|---|---|---|
| QTc (Fridericia) | <= 450 ms | <= 450 ms |
| | > 450 ms | > 450 ms |
| | > 480 ms | > 480 ms |
| | > 500 ms | > 500 ms |

Categorical shift from baseline to worst on-treatment change from baseline for the QTcF:

| Parameter | Baseline category | Worst change from baseline |
|---|---|---|
| QTc (Fridericia) | <= 450 ms<br>> 450 ms<br>> 480 ms<br>> 500 ms | <= 30 ms<br>> 30 ms<br>> 60 ms |

The QTcF will be collected in the eCRF page; if the ECG machine only provides the QT interval corrected with the Bazett formula, the eCRF will use it to automatically calculate the QTcF.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the derivation of worst on-treatment values.

Listings of all participants ECG results will be presented. A flag will be used to indicate which measurements belong to the on-treatment period.

Echocardiogram results from measurements performed at screening and at the end of treatment visit will also be listed.

CCI [redacted]

CCI

[redacted]

## 16.2 Pharmacodynamics

No specific pharmacodynamic analysis will be performed.

## 16.3 Patient Reported Outcome

No patient reported outcome data will be collected.

# 17 References

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# 18 Appendices

## 18.1 Appendix 1 – NCI-CTC Gradable and Non-Gradable Safety Laboratory Test Parameters and Direction(s) of Abnormality

### NCI-CTC gradable parameters

| Laboratory Assessment | Parameters | Name in NCI-CTC | Direction(s) of abnormality |
|---|---|---|---|
| Hematology | Hemoglobin | Anemia/Hemoglobin increased | Low/High |
| | Leukocytes (WBC) | White blood cell decreased / Leukocytosis | Low/High |
| | Neutrophils | Neutrophil count decreased | Low |
| | Lymphocytes | Lymphocyte count decreased / increased | Low/High |
| | Eosinophils | Eosinophila [a] | High |
| | Platelets | Platelet count decreased | Low |
| Biochemistry | Albumin | Hypoalbuminemia | Low |
| | Alanine Aminotransferase (ALT) | Alanine Aminotransferase increased [a] | High |
| | Aspartate Aminotransferase (AST) | Aspartate Aminotransferase increased [a] | High |
| | Alkaline Phosphatase | Alkaline Phosphatase increased [a] | High |
| | Gamma Glutamyl Transferase (GGT) | GGT increased [a] | High |
| | Total Bilirubin | Blood bilirubin increased [a] | High |
| | Amylase | Serum amylase increased | High |
| | Lipase | Lipase increased | High |
| | Creatinine | Creatinine increased [a] | High |
| | Sodium | Hyponatremia / Hypernatremia | Low / High |
| | Potassium | Hypokalemia / Hyperkalemia | Low / High |
| | Calcium | Hypocalcemia / Hypercalcemia | Low / High |
| | Glucose | Hypoglycemia / Hyperglycemia | Low / High |
| Coagulation | Activated Partial Thromboplastin Time | Activated Partial Thromboplastin Time prolonged | High |
| | Prothrombin Intl. Normalized Ration (INR) | INR increased | High |

Note: parameters with both Low and High directions of abnormality are going to be split. For example, Calcium is going to be split in Calcium Low and Calcium High.

[a] on-treatment grading dependent on baseline status.

## NCI-CTC non-gradable parameters

| Laboratory Assessment | Parameters |
|---|---|
| Hematology | Hematocrit |
| | Mean corpuscular volume (MCV) |
| | Mean corpuscular hemoglobin (MCH) |
| | Reticulocytes |
| | Reticulocytes/Erythrocytes |
| | Neutrophils/Leukocytes (%) |
| | Lymphocytes/Leukocytes (%) |
| | Basophils |
| | Basophils/Leukocytes (%) |
| | Eosinophils/Leukocytes (%) |
| | Monocytes |
| | Monocytes/Leukocytes (%) |
| Biochemistry | Total Protein<br>Urea Nitrogen (BUN)<br>Serum cystatin C |
| Coagulation | Prothrombin Time |
| | Prothrombin Time/Standard |
| Urinalysis | Blood |
| | Bacteria (Microscopic analysis) |
| | Casts (Microscopic analysis) |
| | Crystals (Microscopic analysis) |
| | Epithelial Cells (Microscopic analysis) |
| | Bilirubin |
| | Glucose in Urine |
| | Urobilinogen |
| | Ketones |
| | Nitrite |
| | pH |
| | Proteins in Urine |
| | Erythrocytes in Urine (Microscopic analysis) |
| | Leukocytes esterase |
| | Leukocytes in Urine (Microscopic analysis) |
| | Specific gravity |

## 18.2 Appendix 2 – Correspondence between TNM classification, clinical stage and subgroup level

**TNM Classification Version 8**

| Subgroup Level | Stage | T | N | M |
|---|---|---|---|---|
| Advanced | IIIB | T1/T2 | N3 | M0 |
| | | T3/T4 | N2 | M0 |
| | IIIC | T3/T4 | N3 | M0 |
| Metastatic | IV | Any T | Any N | M1 |
| | IVA | Any T | Any N | M1a |
| | IVB | Any T | Any N | M1b |
| | IVC | Any T | Any N | M1c |

**TNM Classification Version 7**

| Subgroup Level | Stage | T | N | M |
|---|---|---|---|---|
| Advanced | IIIB | T1/T2/T3 | N3 | M0 |
| | | T4 | N1/N2/N3 | M0 |
| Metastatic | IV | Any T | Any N | M1 |

T = tumour, N = nodus, M = metastases.

Note: the use of either TNM version 8 or version 7 does not affect the categorization of participants in "Advanced" or "Metastatic".

# ELECTRONIC SIGNATURES

## Document: ctp-ms202202-0002-iap

| Signed By | Event Name | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'GMT'Z) |
|---|---|---|---|
| PPD | Task Completed (Approval eSign): Approved | Business Approval | 21-Apr-2021 12:11 |
| PPD | Task Completed (Approval eSign): Approved | Business Approval | 22-Apr-2021 12:33 |