STATISTICAL ANALYSIS PLAN

Protocol Number: 213152

A Phase Ib Trial to Evaluate the Efficacy and Safety of Bintrafusp Alfa Monotherapy in Metastatic or Locally Advanced/Unresectable Urothelial Cancer with Disease Progression or Recurrence Following Treatment with a Platinum Agent

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 07SEP2022) for Protocol 213152.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	15MAY2020	PPD	Not Applicable – First Version.
0.2	14AUG2020	PPD	Significant changes to align with Merck Bintrafusp Alfa trial analysis plans. See tracked changes.
0.3	11NOV2020	PPD	Updated Section 2.4 for table of endpoints. Added details of exploratory endpoints analysis. Added details of missing date imputations and moved to appendix 2. Updated details for COVID-19 analyses to be consistent with GSK company recommendations.
0.4	04JAN2021 07JUL2022	PPD PPD	Updated references. Significant changes to align with study scope due to Protocol Amendment 02. CCI [redacted]

			change in study scope. The following previously planned analyses were removed: All analyses related to Interim Analysis, CCI CCI CCI and CCI CCI

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol 213152. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on Protocol Amendment 02 dated 03-Mar-2022 and eCRF version 2.0 dated 10-Jun-2020.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. PRIMARY OBJECTIVE

The primary objective is to evaluate the anti-tumor activity per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 in participants with metastatic or locally advanced/unresectable urothelial cancer treated with bintrafusp alfa.

2.2. SECONDARY OBJECTIVE

The secondary objective is:

- Evaluate the safety and tolerability of bintrafusp alfa in participants with urothelial cancer

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2.4. ENDPOINTS

The primary, secondary and exploratory endpoints relevant to analyses to be performed based on this SAP are described in the following table:

Table A: List of Endpoints

Objectives	Endpoints	SAP Section	Analysis Set	Variable
Primary				
Evaluate the anti-tumor activity per RECIST 1.1 in participants with metastatic or locally advanced/unresectable urothelial cancer treated with bintrafusp alfa	Confirmed Overall Response per RECIST 1.1 assessed by investigator.	13.1	Safety/Treated	ORR (by Investigator)
Secondary				
Evaluate the safety and tolerability of bintrafusp alfa in participants with urothelial cancer.	Frequency and severity of AEs using **Error! Reference source not found.**.	14.1.1	Safety/Treated	Treatment Emergent Adverse Events (TEAE)

Objectives	Endpoints	SAP Section	Analysis Set	Variable
CCI [redacted]				

CCI [redacted]; BOR = Best Overall Response; NCI CTCAE= Toxicity Grading based on national Cancer Institute-Common Terminology Criteria for Adverse Events v5; ORR = overall response rate; CCI [redacted] CCI [redacted] CCI [redacted]; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase Ib open-label, global, multicenter, single-arm trial of bintrafusp alfa administered to participants with metastatic or locally advanced/unresectable urothelial cancer with disease progression or recurrence following treatment with a platinum agent.

The primary study objective is to evaluate the ORR per RECIST v1.1. The secondary objective is to evaluate safety and tolerability of bintrafusp alfa.

Participants who permanently discontinue study treatment will enter the follow-up period of the study and undergo the assessments as indicated in Section 8 of the Protocol.

Approximately 25 participants will be treated in this study.

The study includes:

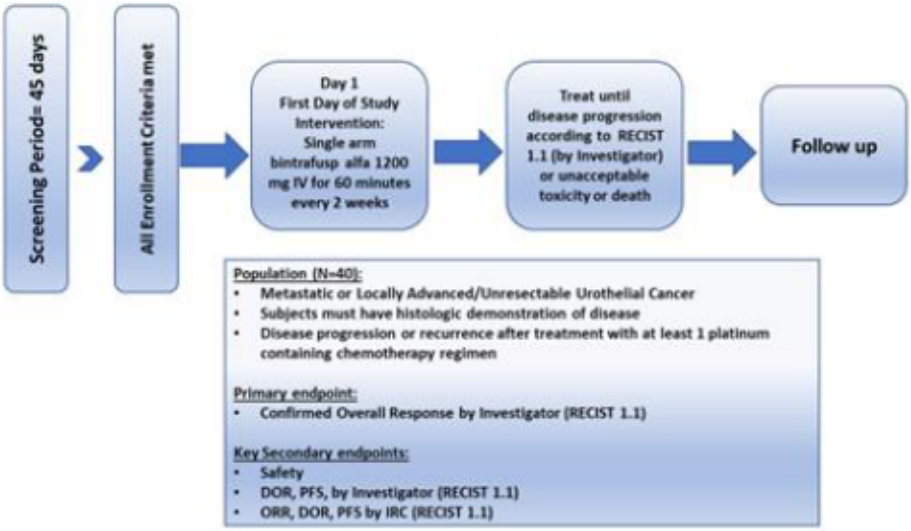
- 45-day screening period
- Treatment with bintrafusp alfa 1200 mg as an IV infusion Q2W until disease progression

as determined by Investigator using RECIST v1.1 (Eisenhauer EA, 2009) death, unacceptable toxicity, study withdrawal, or up to 2 years (see Protocol, Section 7).

- Participants who have experienced a confirmed complete response (CR) can continue treatment for a maximum of 24 months after confirmation of response (at the discretion of the Investigator). If the Investigator believes that a participant with confirmed CR may benefit from treatment beyond 24 months, it may be permissible to continue treatment after discussion with the GSK Medical Monitor.
- Participants with stable disease (SD) or partial response (PR) should continue treatment up to a period of 24 months from first dose until disease progression, or any other discontinuation criterion is met.
- Safety Follow-up: will continue until 12 weeks after the last administration of bintrafusp alfa. The 12-week Safety Follow-up can be conducted via telephone calls or participant chart reviews unless there is medical necessity requiring a clinical visit.
- Long-term Follow-up: should be performed every 12 weeks after the Safety Follow-up according to the Schedule of Activities (see Section 1.3 of the Protocol). Long-term Follow-up should be performed by chart reviews or telephone calls.
- Once the Data Cut-Off (DCO) date for the final analysis for this study has been reached, the clinical study database will be closed to new data and any participants that continue to receive study intervention at this time will be followed as described in Section 8.2 of the protocol.

Biopsies prior to study treatment are required, as described in eligibility criteria (see Protocol Section 5.1). CCI [redacted] CCI [redacted]

Table B: STUDY SCHEMA



3.2. SCHEDULE OF ACTIVITIES

Schedule of activities can be found in Section 1.3 of the Protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

- The term "AEs" in the endpoint "Frequency and severity of AEs" associated with the secondary objective "Evaluate the safety and tolerability of bintrafusp alfa in participants with urothelial cancer" in the protocol, refers to adverse events that begin on or after the start of the study treatment or worsened after the start of the study treatment and therefore are treatment-emergent AEs (TEAEs). TEAEs will be used as the endpoint to be reported in this SAP.
- Due to special circumstances relating to the COVID-19 pandemic, the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare will be applied. For the duration of such special circumstances, the

following may impact the data and analysis:

- Delayed FPI (First Patient In)
- Protocol deviations due to COVID-19
- Missed visits due to COVID-19
- Missed or modified assessments
- Treatment interruptions or delays
- Early study discontinuation or withdrawals due to having COVID-19 or COVID-19 related issues
- Adverse events or SAEs due to COVID-19.

4. PLANNED ANALYSES

All planned analyses identified in this SAP will be performed in a Final Analysis by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan and Database Lock.

5. ANALYSIS SETS

Definitions for analysis sets are provided below.

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5.1. SCREENED ANALYSIS [SCR] SET

The Screened Analysis (SCR) set will contain all participants who sign the ICF.

5.2. SAFETY/TREATED ANALYSIS SET [SAF]

The safety/treated analysis set (SAF) will contain all participants who were administered at least one infusion of bintrafusp alfa.

If there is any doubt whether a participant was treated or not, they will be assumed to have

been treated for the purposes of analysis. This is the primary analysis set for reporting efficacy and safety.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first administration of study treatment (Day 1 is the day of the first administration of study treatment).

- If the date of the event is on or after the reference date, then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date, then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 2; Partial Date Conventions.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last available/non-missing measurement taken prior to reference start date.

- If an assessment is planned to be performed prior to the first administration of study treatment in the protocol and the assessment is performed on the same day as the first administration of study treatment, it will be assumed that it was performed prior to study treatment, if assessment time is not collected or is missing.
- If assessment time is collected, the observed time as well as time of first dose of study

treatment will be used to determine pre-dose on study day 1 for baseline calculation.

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

In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

6.3. DERIVED TIMEPOINTS

6.3.1. ON-TREATMENT PERIOD

The on-treatment period is defined as the time from first study treatment to the last study treatment date plus 30 days or the earliest date of subsequent anticancer therapy minus 1 day, whichever occurs first, unless otherwise stated.

For participants with treatment ongoing at cut-off date, all data from the first study treatment up to the cut-off date will be considered under the on-treatment period.

Any systemic anticancer therapy, any anticancer surgery and any anticancer radiotherapy as documented in the "Anti-cancer treatment after discontinuation" eCRF page will be considered as subsequent anticancer therapy.

In the case of treatment delay, the definition for on-treatment period remains the same.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

For efficacy analyses, unscheduled assessments can be used in the determination of baseline according to Section 6.2. Unscheduled visits post-baseline will be excluded from table summaries CCI [redacted] but will be included in listings.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

Re-screened participants will only be counted once in the SCR, and will consider only the latest screening (screening with the latest informed consent).

6.5. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

6.6. STATISTICAL TESTS

The default significance level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses. In general, continuous variables will be summarized using number and percentage of participants, number and percentage of participants with missing values, mean, standard deviation, median, 25^{th}-75^{th} percentile (Q1-Q3), minimum and maximum. If there are no missing values the number of participants with missing values will be set to 0.

Categorical variables will be summarized using number of participants and percentages. Unless otherwise stated percentages are calculated based on the number of participants in the analysis set of interest and counts of missing observations will be included in the denominator. Counts of missing observations will be included as a separate category in table summaries. For by-visit summaries, denominators will include the number of participants in the analysis set of interest that are still present in the study at that visit.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Change from baseline = timepoint value – baseline value
- Percent Change from baseline = 100 * (timepoint value – baseline value) / baseline value.

Change from baseline will only be calculated when both the timepoint and baseline values are non-missing.

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

There will be no adjustment for covariates in the analysis. In addition, as the study is open-label and only includes one arm, no adjustments will be made for randomization or blinding purposes.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally.

When specified, statistical analysis will be presented by geographic region. Geographic region will be categorized as follows:

Geographic Region	Country
North America	United States, Canada
Europe	UK, Spain, Netherlands, France

7.3. MISSING DATA

Unless otherwise stated, missing data will not be imputed. Missing statistics should be presented as "nd" for "not determined" in tables.

Missing dates (incomplete or partial dates and handling of age calculations, disease history,

AEs, prior and concomitant medications, subsequent anti-cancer therapy and death date) will be handled as per Appendix 2 of this SAP.

Missing efficacy data will be handled as described in Section 13.1.2 and 13.2.3 of this SAP.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

As there is only one primary efficacy endpoint, no adjustments will be made for multiple comparisons.

7.5. EXAMINATION OF SUBGROUPS

There will be no subgroup analyses conducted for this study.

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables [CCI] and listings to be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All participants who provide informed consent will be accounted for in this study.

9.1. DISPOSITION

Participant disposition and withdrawals (including those due to COVID-19), and reasons for exclusion from each analysis set, including inclusion and exclusion criteria will be presented for the SCR set.

The following information will be reported:

- Total number of participants screened (i.e. participants who gave informed consent)
- Number of participants who discontinued from the study prior to study treatment overall and grouped by the main reason (e.g. the failed specific inclusion or exclusion criteria, adverse event, lost to follow-up, protocol non-compliance, death, progressive disease, withdrawal by participant and other)
- Number of re-screened participants
- Number of participants who received at least one dose of study treatment (SAF)
- Number of participants with treatment ongoing at the data cut-off date
- Number of participants off study treatment, grouped by main reason (treatment completed as per protocol, adverse event, lost to follow-up, protocol non-compliance, death, progressive disease, withdrawal by participant and other)
- Number of participants ongoing on the study at the data cut-off date
- Number of participants who completed/discontinued the study participation, with the associated main primary reason (study completed according to protocol, adverse event, lost to follow-up, protocol non-compliance, death, progressive disease, withdrawal by participant and other).

No percentages will be provided for the number of participants screened and re-screened including for the reasons participants discontinued from the study prior to study treatment. All other counts will include percentages based on the number of participants in the SAF.

A participant will be considered to have completed the study if the participant dies or otherwise progresses during the treatment or follow-up period or has been in follow-up for a maximum of 3 years or if they are in follow-up when the DCO date is reached, whichever is sooner.

The number of participants in each analysis set will be summarized overall.

A listing of participant disposition will include participant identifier, date of informed consent, included in the study, first/last study treatment date, date and reason for discontinuation of treatment, date and reason for discontinuation of the study, population flags, rescreened participant ID, date of screen failure and reason for screen failure. When the reason such as reason for discontinuation of treatment will be categorized as "Other, specify" or "Withdrawal by subject, specify", the verbatim text as entered in the eCRF will be

included in the listing. Participants who are re-screened will only be included once, with the details of participant identifier, date of screen failure and screen failure reason.

9.2. PROTOCOL DEVIATIONS

Details of the process for protocol deviation collection, review and finalization and definition of important protocol deviations will be presented in the Protocol Deviations Management Plan.

All protocol deviations classified as important will be listed including those due to COVID-19, if applicable, for the SAF. The listing will include: participant identifier, category of the deviation (e.g. inclusion/exclusion criteria), and a description of the deviation.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the SAF.

No statistical testing will be carried out for demographic or other baseline characteristics.

10.1. DEMOGRAPHICS

The following demographic characteristics will be summarized for this study:

- Age (years) - calculated relative to date of consent
- Age Categories:
  - < 65 years, ≥ 65 years
  - 65-74 years, 75-84 years, ≥ 85 years.
- Sex (male, female)
- Race
  - For participants reporting one race only: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Not collected at the site, Other.
  - For participants reporting several races, all combinations will be reported under

'More than one race" category.

- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Geographic Region (Europe, North America)

Details of alcohol usage and nicotine consumption from the "Alcohol Consumption" and "Nicotine Usage" eCRF forms will be collected at baseline and will be included in a listing of Demographic characteristics including sex, race (all reported races in the case of multiple races and details in the case of "other" race), ethnicity, geographic region, age (years), age category, height, weight and BMI will be presented in a listing. The listing will also include positive history of Tuberculosis (TB) exposure, TB collection date, assay and result.

10.2. DERIVATIONS

- Age (years) = (date of given informed consent – date of birth +1) / 365.25
- Geographic Region will be determined from investigator site codes
- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$.

11. MEDICATIONS

Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD), B3.
See Appendix 2 for handling of partial dates for medications.

11.1. PREVIOUS ANTI-CANCER TREATMENTS AND PROCEDURES

Prior Anti-cancer Therapies will be captured on the "Prior Anti-cancer Drug Therapies" eCRF page and the following will be summarized:

- Participants with at least one previous anti-cancer drug therapy
- Number of any previous anticancer therapy regimens: 0, 1, 2, >2. Also mean, SD, median, Q1, Q3, min and max
- Intent of therapy (including all treatment regimens): Neoadjuvant / Adjuvant / Metastatic or Locally advanced

- Best response of last treatment regimen: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (non-CR/non-PD) / Not Assessable / Unknown / Not applicable
- The time since completion of first-line (1L) of platinum-based treatment will also be summarized. Platinum-based treatment will be identified for participants who received at least one platinum-based drug (cisplatin, oxaliplatin or carboplatin). The time since completion will be measured using the maximum stop date within the identified regimen (maximum start date will be used in case the stop date is not available).
- Number of participants per 1L regimen, e.g., cisplatin/gemcitabine.

If there is a platinum-based treatment with an intent of metastatic/locally advanced, then the first of these will be considered as first-line. Otherwise, the first platinum-based treatment (with intent of adjuvant or neoadjuvant) will be considered first-line.

A listing of previous anti-cancer drugs will include participant identifier, age, sex, race, regimen name, medication(s), start date, end date, intent of therapy, Line Number for Metastatic/Locally Advanced, best response, date of progression and whether Radiotherapy was administered as part of the therapy.

11.2. PREMEDICATIONS FOR BINTRAFUSP ALFA

Premedications are medications administered per protocol on the same day as, but prior to, the study treatment to minimize potential infusion-related reactions.
Premedications will be included in a listing of infusion-related reactions.

12. STUDY TREATMENT EXPOSURE

Exposure to study treatment in weeks will be presented for the SAF.

The date of first study treatment administration will be taken from the eCRF "Bintrafusp Alfa Administration Details" form. The date of last study treatment will be taken from the eCRF "Bintrafusp Alfa Termination" form.

For the analysis of exposure, a dose is regarded to be administered if the actual dose received is > 0mg.

Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

Summaries of exposure will include:

- Duration of treatment (weeks)
- Total number of infusions received
- Cumulative dose (mg)
- Dose intensity (mg/cycle)
- Relative dose intensity (%) as a continuous variable, and categorized as
    - < 80%
    - 80%-90%
    - > 90%.

Study treatment exposure will be included in a listing of study treatment which will include participant identifier, age, sex, race, visit, infusion start date and time, infusion end date and time, infusion rate (mL/hr), actual dose (mg), route, administration modification including dose not given and reason for modification.

12.1. DERIVATIONS

Duration of treatment (weeks) = (date of last dose – date of first dose + 14)/7.

Total number of 2-week cycles is defined as the duration of therapy (weeks) /2.

Cumulative dose (mg) per participant is the sum of the total study treatment that the participant received (actual dose) over the duration of exposure (i.e. total study treatment administered (mg)).

Dose intensity of treatment (mg/cycle) per 2-week cycle is defined as cumulative dose of treatment divided by (duration of treatment (in weeks)/2)

Relative dose intensity is defined as the actual dose intensity divided by the planned dose

intensity per cycle and expressed in a percentage.

13. EFFICACY AND EXPLORATORY OUTCOMES

13.1. PRIMARY EFFICACY

The primary efficacy analysis will be performed on the SAF. Details of tumor assessment based on imaging will be listed and will include: participant ID, age, sex, race, first and last bintrafusp alfa administration date, confirmed best overall response, date for first subsequent anti-cancer therapy, date of death, visit, date of imaging(day), Lesion type, Sum of Lesion Diameters (mm), Change from baseline (%) and overall response. The listing also includes lesion ID, size, status, site, type, method and response for each lesion type, as applicable.

13.1.1. PRIMARY EFFICACY VARIABLE(S) & DERIVATION(S)

The primary efficacy endpoint is the confirmed objective response by the investigator. Overall response rate (ORR) is defined as the percentage (%) of participants with a best overall response (BOR) of PR or CR as assessed by the investigator using RECIST 1.1 out of the total number of participants in the SAF. Tumor response i.e., complete response (CR), partial response (PR), and stable disease (SD), and progressive disease (PD) will be based on the assessments from the investigators' assessment of objective evidence (e.g., radiological scan). Overall responses will be measured in accordance with the RECIST v1.1 (Eisenhauer EA, 2009).

Lesion assessment method and timing, evaluation of disease, disease progression and response criteria will be conducted according to RECIST (version 1.1) as outlined in Section 8.3 of the protocol. 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.

Best overall response (BOR) will be assessed based on the tumor response determined by the investigator at each evaluation timepoint from the first study treatment until the first documented disease progression for RECIST criteria. Only tumor assessments performed before the start of any further anticancer treatment will be considered in the assessment of

BOR. Clinical deterioration will not be considered as documented disease progression.

Confirmed BOR according to RECIST 1.1 (Eisenhauer EA, 2009) will be assessed according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart and before progression.
  - Note: It is reasonable to consider CR-NE-CR or CR-PR-CR as CR as long as the second CR is more than 28 days away from the first timepoint.
- PR = at least two determinations of PR at least 4 weeks apart and before progression (and not qualifying for a CR)
  - Note: It is reasonable to consider PR-NE-PR or PR-SD-PR as PR as long as the second PR is more than 28 days away from the first timepoint.
- SD = at least one SD assessment (or better) $\geq$ 6 weeks after first date of study treatment and before progression (and not qualifying for CR or PR)
- PD = progression $\leq$16 weeks after first date of study treatment (and not qualifying for CR, PR or SD)
- NE = all assessments are NE or participant has a missing (or not evaluable) baseline tumor assessment and/or no (or not evaluable) tumor assessments on-treatment, or participant does not complete any of the following response above.

13.1.2. Missing Data Methods for Primary Efficacy Variable(s)

- Participants with no (or not evaluable) post-baseline data are considered as having a non-evaluable response. No missing dates will be imputed for the primary efficacy variable.

13.1.3. Final Analysis of Primary Efficacy Variable(s)

Confirmed BOR will be summarized as the number and percentage of participants with confirmed CR, PR, SD, PD or NE. In addition, the number of participants achieving objective response will be summarized. The corresponding two-sided 95% Confidence Interval (CI) for ORR will be calculated using the Clopper-Pearson (exact) method (Clopper C, 1934) with exact CI for binomial proportion as computed by default by the FREQ procedure using the EXACT option. There will be no adjustments for multiplicity.

- The following reasons for non-evaluable confirmed best overall response will also be included in the summary:
    - No baseline assessment (if applicable)
    - No post-baseline assessments due to death within 8 weeks after the start of study treatment
    - No post-baseline assessments due to other reasons
    - All post-baseline assessments have overall response "Non-evaluable"
    - New anticancer therapy started before first evaluable post-baseline assessment
    - SD of insufficient duration (<6 weeks after the start of study treatment)
    - No evaluable tumor assessment >16 weeks followed by PD (i.e. tumor assessment of PD was >16 weeks after start of study treatment and there was no evaluable tumor assessment in between)
    - Not determined category may also be added if applicable.

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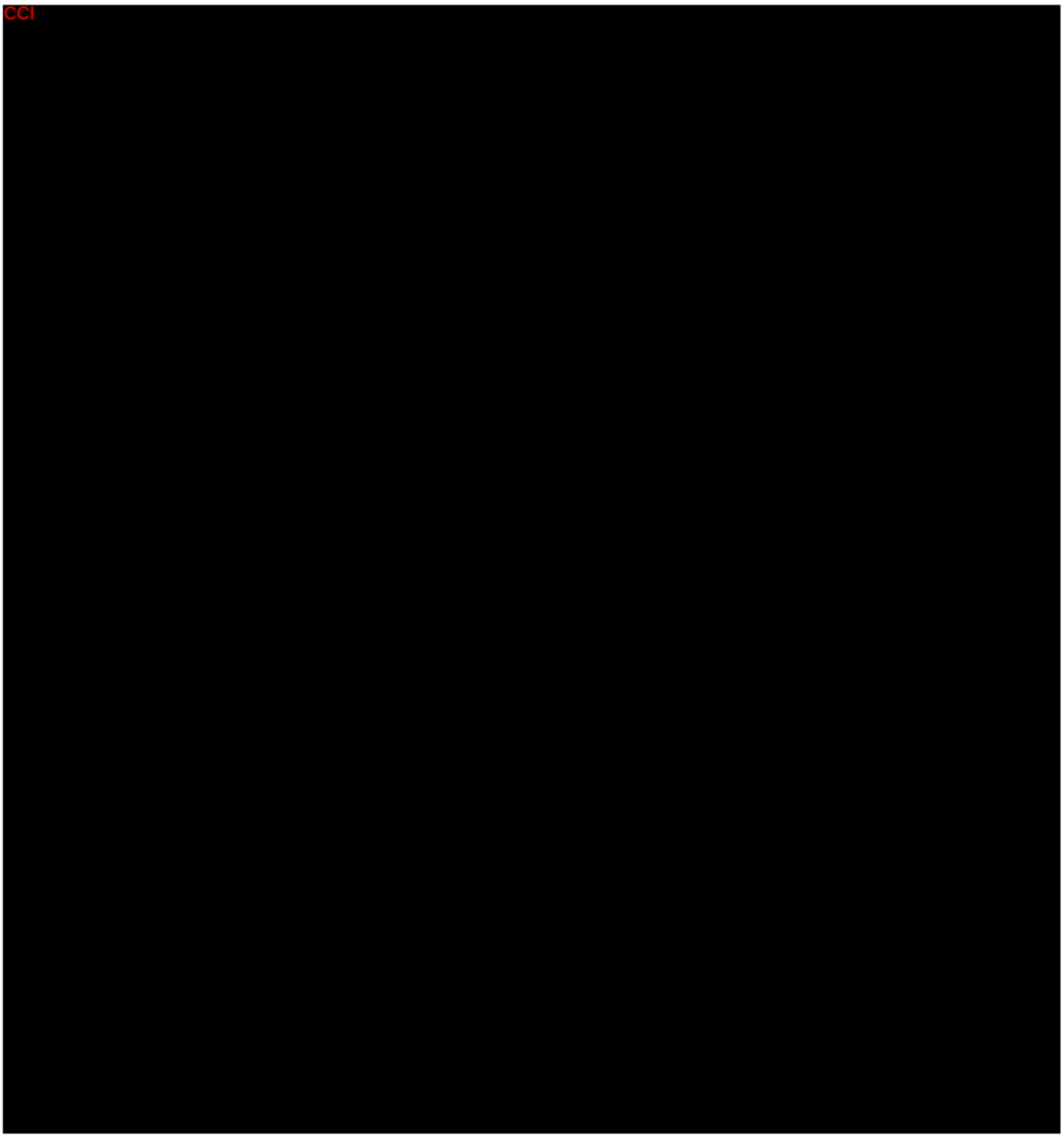

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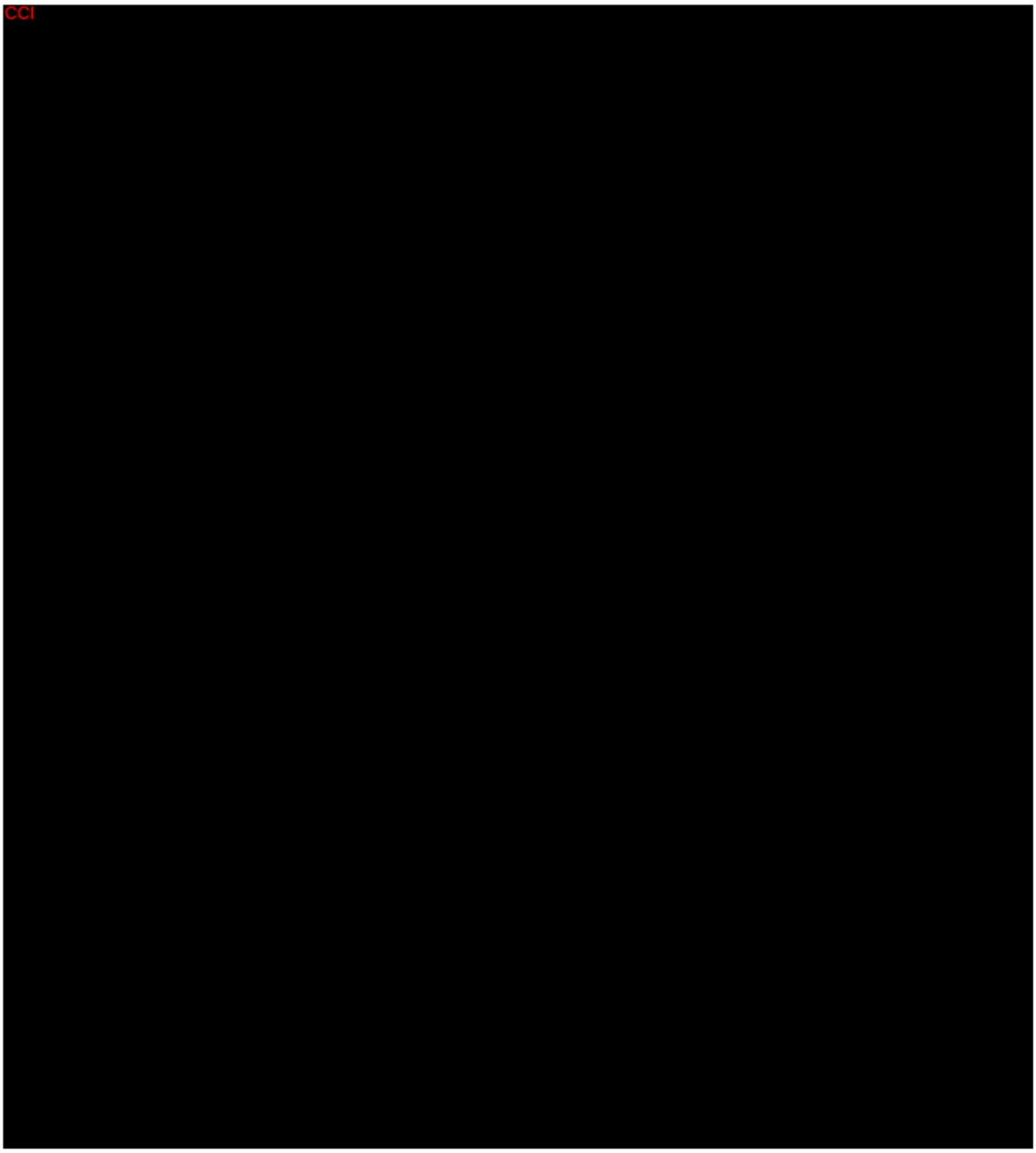

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14. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF.

There will be no statistical comparisons of safety data, unless otherwise specified within the relevant Section.

14.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA V23.0 or later.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity during the on-treatment period, as defined in Section 6.3.1. However, for the first administration of the study treatment, if the AE Start Date is equal to that date, then AEs with the field "Timing related to Bintrafusp alfa" flagged as "Before" on the "Adverse Events Details" form of the eCRF would not be considered a TEAE.

Changes in toxicity grade, seriousness or outcome of AEs are recorded as separate entries in the eCRF with associated end and start dates (start date is equal to or 1 day greater than end date of previous entry). Such entries reporting the same event in such immediately consecutive periods will be considered as one event in the analysis. These events will be kept as separate records in the database and the listing in order to maintain the full detailed history of the events. For tables, the start date of the first treatment emergent record in the sequence is taken as start date of the entire event, similarly the end date of the last event in the

sequence is taken as end date of the entire event. The overall outcome of the adverse event is the outcome of the last event in the sequence. Duration of the AE and the TEAE flag will be adjusted accordingly in the analysis.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst-case; i.e. treatment emergent.

An overall summary of number and percentage of participants within each of the following categories will be provided:

- Any TEAE
- Any related TEAE
- Any serious TEAE
- Any related serious TEAE
- Any grade >=3 TEAE
- Any related grade >=3 TEAE
- Any grade >=4 TEAE
- Any related grade >=4 TEAE
- Any TEAE Leading to Death
- Any related TEAE Leading to Death
- Any TEAE Leading to study termination
- Any related TEAE Leading to study termination
- TEAEs and related TEAEs of special interest:
    - Infusion-related reactions (IRRs)
    - Immune-related AEs (irAEs)
    - Potential TGFβ-mediated skin AEs
    - Treatment related anemia
    - Bleeding events
    - Wound healing
    - Secondary Malignancies

In addition, summary tables of the following TEAE categories will be provided by SOC (ordered alphabetically) and PT (ordered alphabetically):

- TEAEs
- Related TEAEs
- Serious TEAEs
- Related Serious TEAEs
- TEAEs NCI CTCAE severity grade (≥3)
- Related TEAEs NCI CTCAE severity grade (≥3)
- TEAEs leading to death
- Related TEAEs leading to death
- TEAEs Leading to Permanent Treatment Discontinuation
- Related TEAEs Leading to Permanent Treatment Discontinuation

TEAEs and related TEAEs by worst grade will also be summarized.

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

A listing will be provided including all AEs (i.e. TEAEs and Non-TEAEs) and will contain the following information: participant identifier, age, sex, race, first and last date of study treatment, preferred term, reported term for the AE, start date, end date, duration of AE (in days), day relative to the first infusion, day relative to the most recent infusion prior to AE onset, relationship to study treatment, toxicity grade, action(s) taken, outcome, seriousness (Y/N), AESI Type (as detailed in section 14.1.6). AEs outside the on-treatment period (prior or after), will be flagged. Additionally, if the AE occurred on the same day as an infusion, a flag of whether the AE was before, during or after the infusion.

In addition a listing summary of Subject Numbers for Individual TEAEs, sorted by SOC and PT in alphabetical order will be presented.

14.1.1. ALL AEs

Incidence of TEAEs will be presented in frequency tables, sorted by SOC and PT in alphabetical order and, if applicable, broken down further by maximum severity. Each participant will be counted only once within each PT or SOC. If a participant experiences more than one TEAE within a PT or SOC, only the TEAE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of

relationship and severity.

14.1.1.1. Severity

Severity is classified by grade according to the investigator as grade 1 (mild)/ grade 2 (moderate)/ grade 3 (severe)/ grade 4 (life threatening)/ grade 5 (death related to AE)(increasing severity). AEs will be graded using the NCI-CTCAE v5 grading as per the American Society of Clinical Oncology (ASCO) guidelines (NCI-CTCAE v5, 2017). Grading will be recorded in the "Adverse Events" form of the eCRF.

If a participant reports a TEAE more than once within that SOC/ PT, the AE with the worst-case grade will be used in the corresponding summaries. In case a participant had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

14.1.1.2. Relationship to Study Treatment

Relationship to study treatment is determined by the investigator. TEAEs with a missing relationship to study treatment will be regarded as *"Related"* to study treatment. If a participant reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study treatment will be used in the corresponding relationship summaries.

14.1.2. TEAEs Leading to Temporary Treatment Interruption and Withdrawal of Study Treatment

For TEAEs leading to treatment interruption, modification or discontinuation of study treatment, the following incidence rates (frequencies and percentages) will be summarized in an overview table:

- TEAEs leading to temporary treatment interruption
- Related TEAEs leading to temporary treatment interruption
- TEAEs leading to permanent treatment discontinuation
- Related TEAEs leading to permanent treatment discontinuation
- TEAEs leading to infusion rate reduction
- Related TEAEs leading to infusion rate reduction.

TEAEs leading to temporary treatment interruption will be identified by using the response for Action Taken of "Drug Interrupted" on the "Adverse Events Details" page of the eCRF. TEAEs leading to permanent discontinuation of study treatment will be identified by using the response for Action Taken of "Drug Withdrawn" on the "Adverse Events Details" form of the eCRF. TEAEs leading to infusion rate reduction will be identified by using the response for Other Action Taken of "Rate Reduced" on the "Adverse Events Details" page of the eCRF.

14.1.3. TEAEs Leading to Study Termination

TEAEs leading to study termination will be identified by using the response for Other Action Taken of "Led to study termination" on the "Adverse Events Details" page of the eCRF.

14.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the "Adverse Events" form of the eCRF. TEAEs with missing seriousness will be considered as serious.

14.1.5. AEs Leading to Death

TEAEs leading to Death are those events which are recorded as change in grade ="No" and outcome="Fatal" or Grade="Grade 5 or death related to AE" or serious adverse event="Yes" and seriousness criteria include "Results in death" as the response for Outcome on the "Adverse Event Details" form of the eCRF.

14.1.6. AEs Of Special Interest

AEs of Special Interest (AESI) will be identified by a standardized list of MedDRA preferred terms to be updated on an ongoing basis during the study. The AESIs defined for this study are:

- Infusion-related Reactions
- Immune-related AEs
- TGF-β inhibition mediated skin events including skin lesions

- Treatment related Anemia
- Bleeding events
- Wound healing delay
- Secondary malignancies
- Embryofetal toxicities.

Further details of the derivation of the AESI can be found in Appendix 3.

14.1.6.1. Infusion-related Reactions Including Immediate Hypersensitivity

Infusion-Related Reactions (IRRs) are defined as AEs with PTs according to a pre-specified MedDRA search list, and are divided into two subcategories: "reactions" and "signs and symptoms" based on criteria on the timely relationship as detailed in Appendix 3.

The listing of IRRs will display the study drug administration modification details together with the infusion-related adverse event including administration date (day) /time, reason for modification, type of modification, modification start time, use of premedication, IRR AE Preferred Term, IRR AE grade, IRR AE start day /stop day, IRR AE time related to infusion.

14.1.6.2. Immune-related AEs

Immune-related adverse events (irAEs) will be identified programmatically as detailed in Appendix 3.

The frequency table of immune-related AEs by worst grade and PT will be provided.

14.1.6.3. Potential TGFβ-mediated Skin AEs

Identification of skin AEs possibly related to TGFβ inhibition is detailed in appendix 3.

Frequency tables for TGFβ-mediated skin TEAEs leading to permanent treatment discontinuation and serious TGFβ-mediated skin TEAEs will be provided by MedDRA PTs (including both narrow and broad definition PTs).

14.1.6.4. Treatment related Anemia

Treatment related anemia AEs will be identified as described in Appendix 3.

14.1.6.5. Bleeding Events

Bleeding events are classified by the MedDRA SMQ Hemorrhage terms (excluding laboratory terms) and will be summarized separately for TEAEs and related TEAEs by SOC and PT.

14.1.6.6. Wound Healing Delay

Derivation of wound healing delay AEs can be found in Appendix 3..

14.1.6.7. Secondary Malignancies

Details of the determination of secondary malignancies can be found in Appendix 3.

14.1.6.8. Embryofetal Toxicities

Embryofetal Toxicities will not be derived as the occurrence of this AE is not considered a likely event due to measures of contraception and few participants at an age of child-bearing potential.

14.2. DEATHS

All deaths, deaths within 30 days after last dose of study treatment, death within 60 days after first dose of study treatment (for all participants, the first dose will be the first dose of the first treatment phase) as well as the primary reason for death will be tabulated based on information from the "Death" eCRF forms.

The following summaries will be provided:

- Number of deaths

- Number of deaths within 30 days after last dose of study treatment
- Number of deaths within 60 days after first dose of study treatment

Primary reason for death will be included in each of these sections with the following reasons:

  - Progressive disease and/or disease related condition
  - Event unrelated to study treatment
  - Event related to study treatment
  - Unknown.

In addition, date and cause of death will be provided in an individual participant data listing together with following dosing information: participant identifier, age, sex, race, date of first/last study treatment, number of infusions, day relative to the first and the last infusion, primary reason, autopsy (Y/N/U), AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as Grade 5 or Serious resulting in death), flag for death within 30 days of last dose of study treatment and flag for death within 60 days of first dose of study treatment.

14.3. LABORATORY EVALUATIONS

Results from local laboratories will be included in the reporting of this study for Hematology, Biochemistry, Urinalysis, Coagulation, Thyroid Panel and Screening Tests and will be entered in the corresponding eCRF forms. CCI [redacted] CCI [redacted] A list of laboratory assessments to be included in the outputs is included in the Protocol, Section 10.2, Appendix 2, Table 6.

A listing of hematology, biochemistry and coagulation will be created. This listing will include: participant identifier, age, sex, race, first dose date, last dose date, laboratory parameter (SI units), visit, collection date/time/day, International System of Units (SI) value, lower limit of normal (LLN), upper limit of normal (ULN), indicator of normal range (low, normal, high), toxicity term/grade according to NCI-CTCAE (when applicable) and highest/lowest on treatment value flag. Baseline and post-baseline values after the on-treatment period will be flagged. The on-treatment period is defined in Section 6.3.1. The listing will be sorted by participant identifier, parameter and laboratory measurement date.

T4 and TSH will be recorded in the "Hormonal Tests" form of the eCRF. Results will be

included in the listing. Screening tests including pregnancy tests, and serology data will also be listed from the eCRF.

14.3.1. Reference Ranges and CTC Grading for Laboratory Data

Laboratory results will be classified according to the NCI-CTCAE criteria version 5.0 and as specified in Appendix 4. Quantitative laboratory measurements not part of NCI-CTCAE will be compared with the relevant laboratory reference ranges, converted into the International System of Units (SI) and categorized as:

- Low: Below the lower limit of the laboratory reference range
- Normal: Within the laboratory reference range (upper and lower limit included)
- High: Above the upper limit of the laboratory reference range.

14.3.1.1. NCI-CTCAE Gradable Parameters

Parameter	Parameter code	Name in NCI-CTC	Direction of abnormality
Biochemistry			
Alanine Aminotransferase	ALT	Alanine aminotransferase increased	High
Albumin	ALB	Hypoalbuminemia	Low
Alkaline Phosphatase	ALP	Alkaline phosphatase increased	High
Amylase	AMYLASE	Serum amylase increased	High
Aspartate Aminotransferase	AST	Aspartate aminotransferase increased	High
Bilirubin total	BILI	Blood bilirubin increased	High
Calcium[a]	CA	Hypercalcemia/Hypocalcemia[a]	High/Low

Parameter	Parameter code	Name in NCI-CTC	Direction of abnormality
Creatinine	CREAT	Creatinine increased	High
Glucose	GLUC	Hypoglycemia	Low
Lipase	LIPASET	Lipase increased	High
Potassium	K	Hyperkalemia/Hypokalemia	High/Low
Sodium	SODIUM	Hypernatremia/Hyponatremia	High/Low
Hematology			
Absolute lymphocyte	LYM	Lymphocyte count decreased/Lymphocyte count increased	High/Low
Absolute neutrophils	NEUT	Neutrophil count decreased	Low
Hemoglobin	HGB	Anemia/Hemoglobin increased	Low/High
Leukocytes (WBC)	WBC	Leukocytosis/White blood cell decreased	High/Low
Platelets count	PLAT	Platelet count decreased	Low
Absolute Eosinophils	EOS	Eosinophilia	High
Coagulation			
Activated Partial Thromboplastin Time[b]	APTT	Activated partial thromboplastin time prolonged	High
Activated PTT/Standard[b]	APTTSTND	Activated partial thromboplastin time prolonged	High
Prothrombin International Normalized	INR	INR increased	High

Parameter	Parameter code	Name in NCI-CTC	Direction of abnormality
Ratio[b]			

[a] based on corrected calcium
[b] reported on the "Coagulation" eCRF form

For calcium, CTCAE grading is based on corrected calcium. Corrected calcium is calculated from albumin and calcium as follows based on the International System of Units (SI):

Corrected calcium (mmol/L) = measured total calcium (mmol/L) + 0.02 (40 – serum albumin(g/L))

14.3.1.2. Non-gradable Parameters

Parameter (LBTEST)	
Biochemistry	
Bilirubin direct	BILIDIR
Bilirubin Indirect	BILINDIR
Chloride	CL
C-Reactive Protein	CRP
Gamma-glutamyl Transferase	GGT
Total Protein	PROT
Urea Nitrogen	BUN
Hematology	
Absolute Basophils	BASO
Absolute Monocytes	MONO
Absolute Reticulocytes	RETI
Basophils/Leukocytes	BASOLE
Eosinophils/Leukocytes	EOSLE
Erythrocytes (RBC)	RBC
Hematocrit	HCT

Parameter (LBTEST)	
Lymphocytes/Leukocytes	LYMLE
Mean Corpuscular Hemoglobin	MCH
Mean Corpuscular HGB Concentration	MCHC
Mean Corpuscular Volume	MCV
Monocytes/Leukocytes	MONOLE
Neutrophils/Leukocytes	NEUTLE
Reticulocytes/Erythrocytes	RETIRBC
Coagulation	
Prothrombin Time*	PT
Standard Prothrombin Time*	PTS

14.4. ECG EVALUATIONS

Results automatically calculated from the single 12-lead ECG will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- HR (bpm)
- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS).

A listing of ECG values will be provided including participant identifier, age, sex, race, ECG parameter and unit, visit, ECG date/day/time, value, change from baseline and overall

assessment based on investigator's judgement. Baseline values and post-baseline values collected after the on-treatment period will be flagged. Qualitative ECG results will also be provided in the listing.

14.5. VITAL SIGNS

Vital signs will be measured after 5 minutes of rest in a semi-recumbent or supine position. The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Oxygen Saturation by Pulse Oximetry (%)
- Temperature (^{0}C)
- Height (cm) [at screening only]
- Weight (kg)
- BMI (kg/m^2).

A listing of vital signs will be provided including participant identifier, age, sex, race, vital sign parameter, visit, date, time, value, unit and change from baseline. Baseline values, post-baseline values collected after the on-treatment period and potentially clinically significant abnormalities will be flagged. The on-treatment period is defined in Section 6.3.1.

14.6. OTHER SAFETY ASSESSMENTS

14.6.1. PREGNANCY TEST

Results for pregnancy status as collected on the "Pregnancy Test" eCRF form will also be included in the laboratory listing:

- Pregnancy parameter (serum or highly sensitive urine human chorionic gonadotropin (hCG))

14.6.2. PHYSICAL EXAM

Physical Exam data will not be summarized or listed separately. Any abnormal physical

exam findings will be reported as AEs and summarized in the AE section.

REFERENCES

Brookmeyer J, C. J. (1982). A confidence interval for the median survival time. Biometrics, 38, 29-41.

Clopper C, P. E. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26(4), 404-413.

Eisenhauer EA, T. P. (2009). New response evaluation criteria in solid tumors: revised RECIST guidelines (version 1.1). Eur J Cancer, 45, 228-47.

NCI-CTCAE v5. (2017). Retrieved November 20, 2018, from Common Terminology for Adverse Events, Version 5: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

INTRODUCTION

This appendix applies to standards used for outputting tables, listings and figures. It is intended to provide specifications to guide the statistician or statistical programmer in setting up specifications for programming tables, listings and figures.

OUTPUT FILE NAMING CONVENTIONS

File names should only consist of uppercase letters, lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.

As far as possible, output files should be in RTF format, although .DOC files are also permitted.

The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('T' for table, 'L' for listing and 'F' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (eg T14_3_01_1.RTF)

PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter for the United States, otherwise A4.
All listings and tables will be presented in landscape orientation.

The display area will be 9 inches (22.86 cm) by 6 inches (15.24 cm). This display area corresponds to margins of at least 1.25" top and bottom and 0.87" right and left on a landscape page.

The line size (ls) and page size (ps) are not specific, but the technical reference assures a fit using 10 pt Courier font with no additional compression.

FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 10. The font color should be black. No **bolding**, underlining *italics* or subscripting should be permitted. Try to avoid using super-scripts, unless absolutely necessary. Single spacing should be used for all text.

HEADER INFORMATION

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing
- The customer name should appear in row 1, left-aligned
- Page X of Y, with Y being the total number of pages in the output, should appear in row 1, right aligned
- The protocol number should appear in row 2, left-aligned
- The data cut-off date should appear in row 2, right-aligned
- The drug name should appear in row 3, left-aligned
- The data extract date should appear in row 3, right-aligned
- The output identification number should appear in row 4, centered
- The output title should start in row 5, centered

- The output population should appear in row 6, centered. The population should be spelled out in full, e.g. Intention-to-Treat in preference to ITT.
- Row 7 should be a continuous row of underscores ('_') (the number of underscores should equal the linesize)
- Row 8 should be a blank line
- Mixed case should be used for titles
- The output titles should be designed so that they are arranged consistently through all outputs. For example, content (eg Vital Signs) followed by metric (eg Change from Baseline) e.g. Vital Signs – Change from Baseline.
- Titles should not contain quotation marks or footnote references
- The column headings should be underlined with a row of underscores ('_')
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered
- Column headings containing numbers should be centered
- Column headings should be in sentence case
- In general, the population count should appear in the column header in the form "(N=XXX)"
- As a rule, all columns after the first column should have column headings.

TABLE AND LISTING OUTPUT CONVENTIONS

General:

- The first row in the body of the table or listing should be blank.
- The left hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND.
- Numbers in tables should be rounded, not truncated.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned.

- Whole numbers should be right aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
- If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
- All listing outputs should be sorted (preferably by Treatment, Site Number and Subject Number).
- Do not use superscripts and subscripts.
- The width of the entire output should match the linesize.

Univariate Statistics:

- Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum)
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  Minimum and maximum: N
  Mean, median and CV%: N + 1
  SD: N + 2
- Missing statistics, e.g. when they cannot be calculated, should be presented as "nd" for "not determined. For example, if n=1, the measure of variability [e.g. standard deviation (StD)] cannot be computed and should be presented as "nd".

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
  77 (100.0%)
  50 (64.9%)
  0 (0.0%)

Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).

Confidence Intervals:

- As a rule confidence intervals are output to one decimal place more than the raw data, and standard deviations and standard errors to two decimal places more than the raw data
- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
- Boundary values of confidence intervals should be separated by a comma.
- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
- An example is given below:
  (-0.12, -0.10)
  (9.54, 12.91)

P-values:

- P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:

- Ratios should be reported to one more decimal place than the original data.

Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2).

Denominators:

- If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
- Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values

- A "0" should be used to indicate a zero frequency.
- A blank will be used to indicate missing data in an end-of-text table or subject listing.

FOOTNOTE INFORMATION

Footers should be defined as follows:

- A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page
- Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table
- The program path and name and version number (if applicable) and date/time stamp should appear as final footnote at the bottom of the page
- Footnotes should be left-aligned.
- Footnotes should be in sentence case.
- Only "typewriter" symbols are permitted – eg "*", "$", "#", "@", "&" and "+".
- The symbols should appear in the same order as what they are defined in the table or listing, from left to right.

PROGRAMMING INSTRUCTIONS

Programming instructions must appear at the end of each table or listing shell. Programming instructions, where necessary, should follow the table or listing shells, beginning with the words "programming notes" followed by the notes on a new line. These include notes on the output, reminders of how to handle missing values, repeat shells for similar tables etc.

DATES & TIMES

All dates and times will take the form DDMMMYYYY and HH:MM respectively.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For tables, since there is just one treatment group in this study, there will be one column labelled as Overall displayed.

PRESENTATION OF VISITS

For outputs, visits will be presented as they appear (default Long Name) in the dataset.

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Site-participant ID,
- Date (where applicable),

CONVERSION FACTORS

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

- 1 month = 30.4375 days
- 1 year = 365.25 days

DEFINITION OF DURATION

Duration will be calculated by the difference between start and stop date + 1 if not otherwise specified. For example, duration of response (days) = date of PD/death/censoring – date of response + 1.

The time since an event (e.g. time since initial cancer diagnosis) will be calculated as reference date minus date of event + 1. In general, the reference date will be the date of first study treatment.

The time to an event will be calculated by the difference between the time of event and the reference date + 1 if not otherwise specified. For example, survival time (days) = date of death - date of first study treatment + 1.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Unless otherwise listed below, Partial dates will not be imputed and will be presented in the format "_____YYYY". Missing dates imputed according to the guidelines below will be flagged and included in listings.

MISSING DATA HANDLING RULES FOR AGE CALCULATION

Incomplete dates (date of informed consent, date of birth) for the calculation of age will be imputed as follows:

- In case of missing day for at least one date, but month and year available for both dates: the day of informed consent and the day of birth will be set to 1.
- In case of missing month for at least one date, but year available for both dates, the day and the month of informed consent and the day and month of birth will be set to 1.
- In all other cases, the incomplete dates will not be imputed.

MISSING DATA HANDLING RULES FOR DEATH DATE

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 known alive date and the 15th day of the month
- Otherwise it will not be imputed

MISSING DATA HANDLING RULES FOR LAST CONTACT DATE

The date of last contact will be determined using the following dates (with dates past the cut-off ignored by the derivation):

- All participant assessment dates
- Start and end dates of anticancer therapies administered after study treatment discontinuation.
- AE start and end dates
- Last known alive date collected on the 'Subject Status / Survival Follow-Up' eCRF form (do not use follow up date)

- Study drug start and end dates.

MISSING DATA HANDLING RULES FOR ADVERSE EVENTS

Incomplete AE-related dates will be imputed as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study treatment then the onset date will be imputed by the minimum of start of study treatment and AE resolution date (if not missing).
- In all other cases, the missing onset day or missing onset month will be imputed by 1.
- Incomplete stop dates will be imputed 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.

MISSING DATA HANDLING RULES FOR SUBSEQUENT ANTICANCER THERAPY

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

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

MISSING DATA HANDLING RULES FOR PREVIOUS MEDICATIONS, CONCOMITANT MEDICATIONS AND PRIOR ANTICANCER THERAPIES OR PROCEDURES

Incomplete dates for previous and concomitant medications will be imputed as follows:

For start date of medication:

- If the day is missing, it will be imputed to the 1st day of the month.
- If both day and month are missing, the month and day will be imputed as January

1st.

- If the date is completely missing, no imputation will be performed.

For end date medication:

- If the day is missing, it will be imputed to the last day of the month.
- If both day and month are missing, the month and day will be imputed as December 31st
- If the date is completely missing, no imputation will be performed.

Note: In case the imputation results in a date later than the date of participant's death, then the date of death will be used to impute the incomplete stop date.

APPENDIX 3. ADVERSE EVENTS OF SPECIAL INTEREST

Details of the algorithms for identifying adverse events of special interest can be found in the document AESI algorithms.docx.

APPENDIX 4. CTCAE GRADING CRITERIA

See document: CTC V5.0 guidance.xlsx

CTC V5.0
guidance.xlsx

APPENDIX 5. ABBREVIATIONS

1L	First Line
CCI [redacted]	
ACS	Abnormal, Clinically Significant
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ANCS	Abnormal, Not Clinically Significant
APTT	Advanced Partial Thromboplastin Time
ASCO	The American Society of Clinical Oncology
BMI	Body Mass Index
BOR	Best Overall Response
bpm	Beats Per Minute
C	Celsius
CI	Confidence Interval
Cm	Centimeter
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	
CCI [redacted]	
ECG	Electrocardiogram
eCRF	electronic Case Report Form
FDAAA	Food and Drug Administration Amendments Act
FPI	First Patient In
GSK	GlaxoSmithKline
HCG	Human Chorionic Gonadotropin
HR	Heart Rate
IC	Informed Consent
CCI [redacted]	
IR	Immune-related
irAE	Immune-related AEs
IRC	Independent Review Committee
IRR	Infusion Related Reactions
kg	Kilogram(s)
LLN	Lower Limit of Normal
m	Metre

MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
mmHg	Millimeters of Mercury
msec	Miliseconds
NCI-CTCAE	National Cancer Institute - Common Toxicity Criteria for Adverse Events
ND	Not Determined or No Disease
NE	Non Evaluable
NR	No Result
ORR	Objective Response Rate
CCI	
PD	Progressive Disease
PD-L1	Programmed Death-Ligand 1
CCI	
CCI	
PR	Partial Response
PT	Preferred Term
Q2W	Every 2 Weeks
QT	QT Interval
QTcF	QT interval duration corrected Fridericia's
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety/Treated Analysis Set
SAP	Statistical Analysis Plan
SCR	Screened Analysis set
SD	Stable Disease
SI	International System of Units
SOC	System Organ Class
StD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary