STATISTICAL ANALYSIS PLAN

CIBI308A102

AN OPEN-LABEL, PHASE 1B MULTICENTER STUDY OF IBI308 IN SUBJECTS WITH ADVANCED/METASTATIC SOLID MALIGNANCIES

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.2 (Dated 05Jan2021) for Protocol CIBI308A102 version 6, dated 7Jan2019.

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OUTPUT TEMPLATES SIGNATURE PAGE

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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	18Sep2018	[redacted]	Not Applicable – First Version
0.2	12Jul2019	[redacted]	- The department and position of the responsible person have been changed. - Updates made due to protocol amendment. - The efficacy population is replaced with full analysis set for all efficacy analysis. - Removed the preliminary evaluation due to sponsor strategy. - Added protocol deviations/violations categories. - The medical history and concomitant illness will be summarized by body system instead of MedDRA.
1.0	13Jan2020	[redacted]	Finalized Version
2.0	20Mar2020	[redacted]	- Added derivations for Time Since Initial Diagnosis and Time Since Current Diagnosis. - Added ATC2/ATC3 for prior and concomitant medications summary. - Removed variable of duration of stable disease (DOS). - Added CTCAE grade criteria and shift table of laboratory test results from baseline to worst CTCAE Grade. - Added summary and derivation for QTcF. - Added summary and derivations for Treatment-Induced ADA, Treatment-Boosted ADA, and ADA incidence. - Added summary and criteria of abnormalities for vital sign.

2.1	15May2020	[redacted]	- Added 2nd final analysis due to COVID-19 issue.
2.2	05Jan2021	[redacted]	- Added the PFS rate at 12-week, 24-week, and 36-week. - Converted into SI unit for height and weight. - Updated WHO-DDE version.

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol CIBI308A102. 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 CIBI308A102 version 6, dated 7Jan2019.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to evaluate preliminary anti-tumor activity (objective response rate, ORR) of IBI308 monotherapy in subjects with advanced/metastatic solid malignancies.

2.2. SECONDARY OBJECTIVES

The secondary objectives are

- To measure progression-free survival rate (PFS).
- To measure duration of response (DOR).
- To measure overall survival rate (OS).
- To obtain safety and toxicity data.
- To further evaluate pharmacokinetics (PK) of IBI308.
- To further evaluate immunogenicity of IBI308.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are

- To explore the relationship between baseline markers (PD-L1, TMB etc.) and clinical response
- To explore the relationship between exposure and efficacy/safety
- To assess the impact of ADA on PK, efficacy/safety

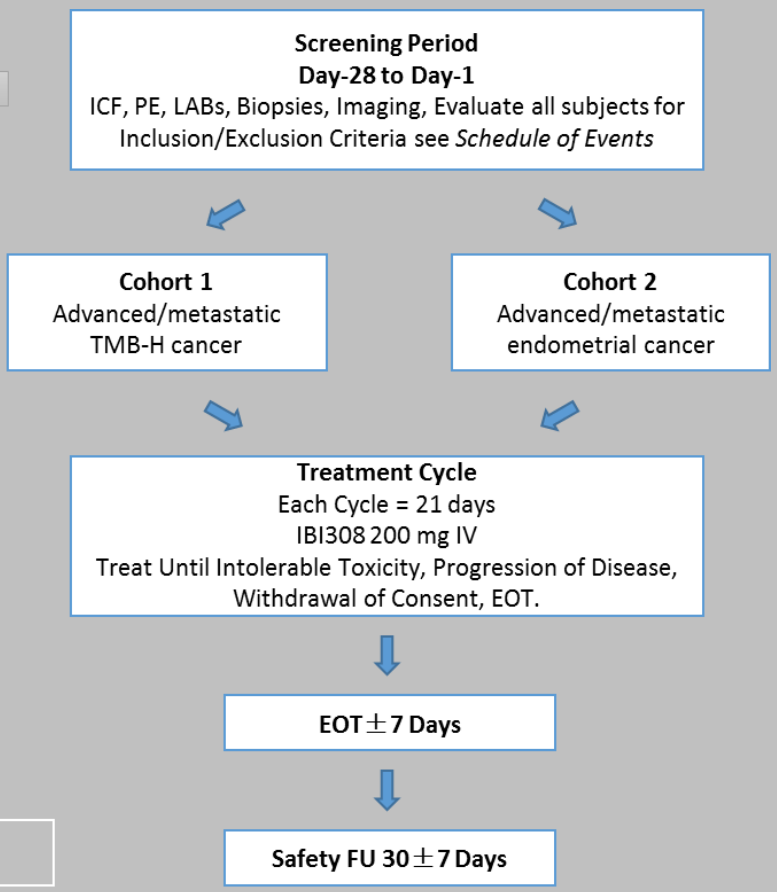
3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is an open-label, phase 1b multicenter study of IBI308 in subjects with advanced/metastatic solid malignancies. The trial will recruit 2 cohorts: cohort 1 consisting of subjects with advanced/metastatic cancer subjects with TMB>10 mutations per megabase (mut/Mb) and cohort 2 consisting of advanced endometrial cancer subjects (refer to Study Design Scheme, and Table B for sample sizes). Sponsor has made strategic decisions to stop enrollment in cohort 1 in this protocol amendment. In each cohort a fixed dose of 200 mg IBI308 will be administered Q3W to the subjects. Additional cohorts may be added to this study via a new IND package or will be added with a protocol amendment submission during the clinical trial stage.

Table A: Scheme of The Study design

Study Schema



EOT= End of Treatment
FU= Follow up

Table B: Study population, sample size and treatment dose

Cohort Number	Indication	Patient Number	IBI308 Dose
Cohort 1	Advanced/metastatic cancers with TMB level >10mut/Mb	2 enrolled as of 7Jan2019	200 mg
Cohort 2	Advanced/Metastatic Endometrial Cancer	40	200 mg

3.2. DETERMINATION OF SAMPLE SIZE

For cohort 2: Assuming the true ORR in advanced/metastatic endometrial cancer subjects receiving IBI308 is 25%, there is an approximately 80% chance to observe 8 or more than 8 responders in a total of 40 subjects (i.e. observed ORR≥20%). With observing at least 8/40 responders, this study will have approximately 96% confidence to exclude ORR≤10%. A preliminary evaluation of efficacy will be conducted after approximately 20 evaluable subjects with at least post baseline 2 tumor assessments. If overwhelming efficacy is observed, this cohort might be further expanded beyond planned 40 subjects to confirm the efficacy observed.

3.3. SCHEDULE OF EVENTS

Schedule of events can be found in Table-1 of the protocol.

3.4. CHANGES TO ANALYSIS FROM PROTOCOL

PK analysis defined in the protocol secondary objectives is not awarded to IQVIA. Date of acknowledgement of the change is 4May2018.

FAS will be considered for all efficacy analysis. Definition of FAS is same as Efficacy population stated in protocol.

Hematology and Biochemistry laboratory quantitative parameters will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 for shift from baseline table.

4. PLANNED ANALYSES

The following formal analysis is planned for the study:

4.1. FINAL ANALYSIS

Two final analyses will be performed by IQVIA Biostatistics following sponsor authorization of the final SAP.

The 1st final analysis will be performed based on 1st database lock on 21May2020. Not all of the data is clean as there is a lack of site accessibility due to Coronavirus (COVID-19) pandemic.

The 2nd final analysis will to be performed based on 2nd database lock when all source data verified, which will be an update with results from both final analyses being addressed in clinical study report.

5. ANALYSIS SETS

All summaries will be presented by assigned cohort. Protocol Table-A contains a detailed presentation of each study cohort.

5.1. ENROLLED ANALYSIS SET [ENR]

The enrolled population will contain all subjects who signed Informed consent.

5.2. SAFETY ANALYSIS SET [SAF]

The safety population will contain all eligible subjects who receive at least one dose of investigational drug. The safety population will be the primary population for evaluating treatment administration, compliance and safety data in the study.

If there is any doubt whether a subject was treated, they will be assumed treated for analysis purpose.

5.3. FULL ANALYSIS SET [FAS]

The full analysis set will include all subjects who complete at least 1 cycle of treatment and have at least 1 post baseline tumor assessment of efficacy or discontinue study early due to progressive disease.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE DATE AND STUDY DAY

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

Reference date is defined as the day of the first dose of study medication (Day 1 is the day of the first dose of study medication), and will appear in every listing where an assessment date or event date appears.

- 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.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). 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, i.e., treatment-emergent or concomitant ("worst case" approach).

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the best/worst case value where required (e.g. shift table).

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

For any subject with early withdrawal assessments available, all early withdrawal assessments related to the specific subject are to be considered in chronological order and are to be:

- Considered as unscheduled.
- Not summarized in the by-visit summaries.
- Only listed in the by-subject data listings.

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

6.4. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

6.5. STATISTICAL TESTS

No formal statistical tests will be performed for this study. The default significance level will be 5%; 95% confidence intervals (CI) will be presented unless otherwise specified in the description of the analyses.

6.6. COMMON CALCULATIONS

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

- Test Value at Visit X – Baseline Value.

The time from Date of Event A to Date of Event B (years) is calculated as:

- (Date of Event B - Date of Event A + 1)/365.25.

The time from Date of Event A to Date of Event B (months) is calculated as:

- (Date of Event B - Date of Event A + 1)/30.4375.

6.7. SOFTWARE VERSION

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

6.8. MISSING DATA

Neither missing safety nor efficacy data will be imputed, with the exception of section 10.1 (demographic data), 12.1 (prior and concomitant medication data), 12.2 (prior and concomitant non-drug treatment data),

15.1 (adverse event data).

7. 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, figures and listings to be provided by IQVIA Biostatistics.

8. DISPOSITION AND WITHDRAWALS

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

Subject disposition and withdrawals will be presented for all eligible subjects.

9. PROTOCOL DEVIATIONS/VIOLATIONS

Protocol deviation will be collected by clinical team and entered into clinical trial management system (CTMS). The protocol deviation will be presented in listing including date, severity and type and will be further summarized for SAF. The type of protocol deviations may include the following categories based on IQVIA SOP:

- Informed Consent Criteria
- Eligibility and Entry Criteria
- Concomitant Medication Criteria
- Laboratory Assessment Criteria
- Study Procedures Criteria
- Serious Adverse Event Criteria
- Visit Schedule Criteria
- Investigation Produce Compliance
- Efficacy Criteria
- Administrative Criteria
- Source Document Criteria
- Regulatory or Ethics Approvals Criteria

- Other criteria- Monitor to enter description

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent
- Sex
  - Female
  - Male
- Is the subject a woman of childbearing potential
  - No
  - Yes
- Reasons for no childbearing potential for woman subject
  - Menopausal
  - Sterilized
  - Other
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not Reported
  - Unknown
- Race
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Naive Hawaiian or Other Pacific Islander
  - White
  - Other
- Baseline Weight (kg)

- Baseline Height (cm)
- Baseline Body Mass Index (BMI) (kg/m^2)
- Baseline Coagulation
  - Was Coagulation Performed: Yes/No
  - Activate Partial Thromboplastin Time (aPTT)
  - International Normalized Ratio (INR)
- Hepatitis and HIV Screen
  - Was Hepatitis and HIV Testing Performed: Yes/No
  - HBsAg: Positvie/Negative
  - HBsAb: Positive/Negative
  - HBcAb: Positive/Negative
  - Hep C RNA (copies/mL)
  - HIV: Positive/Negative
- Baseline Cardiac Assessment (ECHO or MUGA)
  - Was ECHO or MUGA Examination Performed: Yes/No
  - ECHO or MUGA: ECHO/MUGA
  - LVEF (%)
  - Result: Normal/Abnormal, Not Clinically Significant/Abnormal, Clinically Significant
- Baseline Bone Scan
  - Was Bone Scan Performed: Yes/No
  - Any Bone Metastases: Yes/No
  - Location of Metastases: XXX/XXX/XXX
  - Total Number of Lesions(s): 0/1/2/>=3
- Time Since Initial Diagnosis (months)
- Initial Disease Stage
  - Stage I
  - Stage II
  - Stage III
  - Stage Iva
  - Stage IVb
- Time Since Current Diagnosis (months)

- Current Disease Stage
  - Stage I
  - Stage II
  - Stage III
  - Stage Iva
  - Stage IVb
- Histologic Types of Cancer
- Histologic Grading of Cancer
- Value of Tumor Mutational Burden (TMB) (mut/Mb)
- Tumor Mutational Burden (TMB) Level
  - >10 and <15 mut/Mb
  - >=15 and =<20 mut/Mb
  - >20 mut/Mb
  - NA – Cohort 2
- MMR Status (For Cohort 2 Only)
  - dMMR
  - iMMR
  - Unknown
- MSI Status (For Cohort 2 Only)
  - MSI-H
  - MSI-L
  - Unknown
- POLE-ultra-mutates Status (For Cohort 2 Only)
  - Yes
  - No
  - Unknown

10.1. DERIVATIONS

- Height (cm) = height (inches) x 2.54
- Weight (kg) = weight (lbs) x 0.454

- BMI (kg/ m^2) = weight (kg)/ [height (cm)/100]^2
- For all durations calculated relative to the date of informed consent, the following formula will be used. Age calculation is automatically performed in the EDC system:
  - Duration (Years) = (Date of Informed Consent Signed – Date of Event + 1)/365.25
  - For partially missing dates, the above calculation will be based on imputed values. For all calculation elements, if the date part is missing while year and month present, the 15th of the month will be used. If both date and month part are missing while year is present, July 1 will be used for imputation.
- Time Since Initial Diagnosis (months) = (Date of Informed Consent Signed – Date of initial diagnosis date)/30.4375.
- Time Since Current Diagnosis (months) = (Date of Informed Consent Signed – Date of current diagnosis date)/30.4375. If current diagnosis date is later than date of informed consent signed, the time since current diagnosis will be imputed as 0.

11. MEDICAL HISTORY AND CONCOMITANT ILLNESS

Medical history and concomitant illness will be presented for the SAF.

Medical history and concomitant illness data are captured on the 'Medical History' CRF page.

Medical history is defined as those conditions which stop prior to initial treatment of IBI308; concomitant illnesses are conditions which started prior to the date of initial treatment of IBI308 and stopped at or after the date of initial treatment of IBI308.

The summary of medical history and concomitant illness tables will be presented by number and percentage of subjects by body system; each subject could have medical histories under multiple body systems; each subject will be counted only once within each body system.

12. MEDICATION AND PROCEDURES

12.1. PRIOR AND CONCOMITANT MEDICATIONS

Medications used from signed informed consent through visit of safety follow-up 30 days after last dose of study drug will be collected on CRF page "Concomitant/Prior Medications". Concomitant medications are

defined as medications administered after the first administration of the IBI308 or are ongoing at the time of start of treatment.

Medications with the stop dates prior to the date of first dose of the IBI308 will be considered prior medications. All other medications will be considered concomitant.

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE), Version 01MAR2019.

Prior and concomitant medications will be summarized by ATC Level 3, ATC Level 2, and preferred WHO-DDE drug name and listed for the SAF respectively.

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, post concomitant, the medication will be classified by the worst case; i.e. concomitant.

12.2. Prior and Concomitant Non-Drug Treatments (Procedures)

Procedures performed from signed informed consent through visit of safety follow-up 30 days after last dose of study drug are captured on CRF page “Concomitant Non-Drug Treatment”. Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 22.0 (MedDRA 22.0) will be used for coding.

Non-drug treatments (procedures) with the stop dates prior to the date of first dose of the IBI308 will be considered prior non-drug treatments (procedures). All other non-drug treatments (procedures) will be considered concomitant.

Relevant information for non-drug treatments (procedures) will be listed for the SAF.

12.3. Prior and Concurrent Anti-Cancer Therapies and Surgeries

Prior and concurrent anti-cancer therapies includes prior/concurrent anti-cancer radiotherapy, prior/concurrent anti-cancer treatment regimens and prior/concurrent anti-cancer surgical procedures.

Data will be captured on ‘Prior Anti-Cancer Radiotherapy’, ‘Prior Anti-Cancer Treatment Regimens’, ‘Prior Anti-Cancer Surgical Procedures’ CRF pages when only therapies and procedures starting prior to screening visit will be collected. Otherwise the therapy will be presented together with concomitant medications whilst procedures will be considered concomitant procedures in ‘Anti-Cancer Radiotherapy’, ‘Anti-Cancer Treatment Regimens’, and ‘Anti-Cancer Surgical Procedures’ CRF pages, respectively.

All prior and concurrent anti-cancer therapies will be presented in listing. The following information for prior and concurrent anti-cancer therapies will be summarized:

- Prior and Concurrent Anti-Cancer Radiotherapy
  - Was Any Prior Radiation Performed
  - Radiation Therapy Type
  - Treatment Intent
  - Setting
  - Modality Type
  - Radiation Relative Location(s) Category
  - Best Overall Response
- Prior and Concurrent Anti-Cancer Treatment Regimens
  - Were Any Prior Cancer Treatment Regimens Taken
  - Type of Treatment
  - If Chemotherapy or Immunotherapy or Biotherapy or Targeted Agents or Hormonal Therapy, Type of Treatment Administered
  - Number of Lines of Treatment
  - Best Response
  - Medication Term
  - Reason for Discontinuing This Prior Treatment
- Prior and Concurrent Anti-Cancer Surgical Procedures
  - Were Any Prior Surgical, Therapeutic or Diagnostic Procedures Performed
  - Reported Name of Procedure
  - Purpose of Procedure
  - Any Residual Disease Left After the Procedure Performed

13. STUDY MEDICATION EXPOSURE

A fixed dose of 200 mg IBI308 will be administered as IV infusion on day 1 for every three weeks (Q3W) to the patient until disease progression or intolerable toxicity, death, withdrawal of consent, or end of study up to 2 years, whichever occurs first. The date of first study medication administration will be taken from the eCRF “Administration of IBI308” form. The date of last study medication will be taken from the eCRF “End of Treatment” form.

The following dosage information will be summarized for the SAF.

- Total number of IBI308 infusion received
- Total cumulative dose (mg)

- Duration of IBI308 (cycle)
- Dose intensity (mg/cycle)
- Relative dose intensity of IBI308 (%)

13.1. DERIVATIONS

- The total cumulative dose (mg) is defined as the sum of all recorded (scheduled or unscheduled) doses.
- The duration of IBI308 (cycle) is defined as (Date of last dose of IBI308 - date of first dose of IBI308 + 21)/21.
- The dose intensity (mg/cycle) is defined as the total cumulative dose (mg) / duration of IBI308 (cycle).
- The relative dose intensity of IBI308 (%) is defined as the dose intensity of IBI308 defined in the preceding formula divided by 200 mg per cycle (i.e., the planned dose as assigned in the protocol) multiply by 100.

14. EFFICACY OUTCOMES

Treatment efficacy will be evaluated using the following anti-cancer activity parameters.

- Best overall response (BOR) [complete response (CR), partial response (PR), stable disease (SD), or progressive disease]
- Objective response rate (ORR) (CR + PR)
- Duration of response (DOR)
- Disease control rate (DCR) (CR, PR or SD)
- Progression-free survival (PFS) and overall survival (OS)

Tumor assessment will be performed at baseline, every 2 cycles thereafter, and at the end of treatment by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Treatment response will also be assessed by immune RECIST (iRECIST) criteria to assess the potential for pseudo progression.

Anti-cancer activity parameters will be presented by cohort and total group on the FAS.

14.1.1. BEST OVERALL RESPONSE

The BOR is defined as the best response from the date of first study drug administration until documented

RECIST progression, irrespective of whether subjects discontinued treatment. In the absence of RECIST progression, BOR is determined using visit responses up until the last evaluable overall visit response. CR or PR response(s) after receiving subsequent anti-cancer therapy will not be included.

A subject's BOR will be determined as the best response across all time points following CR> PR> SD> PD. When SD is believed to be best response, it must also meet the specified minimum time from Baseline (at least 6 weeks from treatment initiation). If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered unevaluable.

In addition, the following special scenario shall be considered for the determination of BOR: if a subject receives new anti-cancer treatment(s), for that subject, tumor assessments after the first new anti-cancer treatment (same day inclusive) will be considered inadequate thus not counted towards the determination of BOR.

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time-point.

Tumor responses data are captured on 'Tumor Assessments' of CRF Folder, including "Tumor Result: Targeted Lesion", "Tumor Result: Targeted Lesion Follow Up", "Tumor Result: Non-Targeted Lesion", "Tumor Result: Non-Targeted Lesion Follow Up", "Tumor Result: New Lesion" and "Disease Response (RECIST v1.1)", "Disease Response (iRECIST v1.1)". The numbers and the percentages of subjects achieving each category of BOR (CR, PR, SD, PD, NE) will be summarized for the efficacy population. The tumor location, the assessment methods of target lesion, and the overall response for each cycle will also be presented in listing.

According to RECIST v1.1, in non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not result of measurement error.

Confirmed responses (CR or PR) are those responses which are confirmed at a repeat tumor evaluation at least 4 weeks (28 days) after being first observed. The detail derived logic is presented as below, according to the revised RECIST v1.1.

Best Overall Response Based on RECIST v1.1 when Confirmation of CR and PR Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD

CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
CR	NE followed by CR	CR
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	One or more NE/SD followed by PR	PR
NE	NE	NE

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

14.1.2. Objective Response Rate (ORR)

Objective response rate will be the proportion of subject with a BOR of confirmed CR or confirmed PR. The ORR and its 95% confidence interval (CI) will be presented. The 95% exact (Clopper-Pearson) CI will be calculated based on the binomial method.

14.1.3. Disease Control Rate (DCR)

Disease control rate is defined as the proportion of subjects who achieve confirmed CR, confirmed PR, and durable SD based on RECIST v1.1. The DCR as well as 95% exact CI will be estimated.

14.1.4. DURATION OF RESPONSE

Duration of response for responders (subjects with confirmed CR or confirmed PR) is defined as the time interval between the date of the earliest qualifying response and the date of disease progression or death for any cause, whichever occurs earlier. For subjects who are alive without disease progression following the qualifying response, duration of response will be censored on the date of last evaluable tumor assessment.

Kaplan Meier methodology will be used to estimate median duration of response or duration of stable disease and its 95% confidence interval.

14.1.5. PROGRESSION FREE SURVIVAL (PFS)

Progression-free survival is defined as the time from the date of first study dose to disease progression or death whichever occurs first in subjects. Subjects without event (no disease progression or death) will be censored at the date of 'last tumor assessment'. Subjects for whom no post-baseline tumor assessments are available are censored at the time of first dose.

Kaplan Meier methodology will be used to estimate median PFS and its 95% confidence interval, also for the survival rates at week 12, 24 and 36. Kaplan Meier curves will be constructed to provide a visual description of the PFS change with time.

14.1.6. OVERALL SURVIVAL (OS)

Overall survival is defined as the time from the date of the first study dose to the date of death (any cause). Subjects who were alive at the time of analysis or end of study will be censored at the date of the last available visit.

Kaplan-Meier methodology will be used to estimate the median survival time and its 95% confidence interval, also for the survival rates at week 6, 12, 18, 24, 30 and 36. Kaplan Meier curves will be constructed to provide a visual description of the OS change with time.

15. SAFETY OUTCOMES

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

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

15.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA, Version 22.0.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication.

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

An overall summary of AEs table will be provided as specified in the templates. The overall summary of AEs table will include the frequency (number and percentage) of subjects with each of the following by cohort and total group:

- TEAEs
- Treatment-Related TEAEs
- Grade ≥ 3 TEAEs
- Grade ≥ 3 Treatment-Related TEAEs
- Serious TEAEs
- Serious Treatment-Related TEAEs
- Infusion Related Reaction (IRR)
- Immunotherapy-Related Adverse Events (irAE)
- TEAEs Leading to Drug Interrupted
- TEAEs Leading to Drug Withdrawn
- TEAEs Leading to Death

Listings will include TEAEs and Non-TEAEs.

15.1.1. ALL TEAES

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to study medication.

15.1.1.1. Severity

The severity of all TEAEs will be graded according to 5 grades (Grade 1 to Grade 5) (increasing severity) in accordance with the national cancer institute common terminology criteria for adverse event (NCI-CTCAE) V4.03. If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst

case severity will be used in the corresponding severity summaries.

15.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as "Not Related", "Related" (increasing severity of relationship). TEAEs with a missing relationship to study medication will be regarded as "Related" to study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

15.1.2. Immune Related Adverse Events (irAE)

Checkpoint inhibition is associated with a wide spectrum of side effects defined as immune-related adverse events (irAE). IrAEs may include gastrointestinal, hepatic, endocrine, dermatologic and inflammatory events. IrAEs are defined as AEs of unknown etiology potentially associated with an immune phenomenon.

IrAE can be identified on the Adverse Event CRF page with question "Was this an immunotherapy-related adverse event (irAE)?". Summaries of incidence rates (frequencies and percentages) of irAE by SOC and PT will be prepared.

15.2. Deaths

If any subjects die during the study as recorded on the "Death Detail" page of the CRF, the information will be presented in a data listing.

15.3. Laboratory Evaluations

Results from the local laboratory will be included in the reporting of this study for Hematology including CBC with differential, blood chemistry, thyroid tests (TSH, free T3 and T4), urine pregnancy test, urine analysis. The following laboratory parameters will be reported for this study:

- Hematology: Haemoglobin, White Blood Cell Count, Neutrophil (absolute value), Lymphocyte (absolute value), Monocytes (absolute value), Basophil (absolute value), Eosinophil (absolute value), Red Blood Cell Count, Hematocrit, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), Platelet Count
- Blood chemistry: Alkaline Phosphatase, ALT, AST, Total Bilirubin, BUN, Creatinine, Total Protein, Albumin, Fasting Glucose, Potassium, Sodium, Chloride, Uric Acid, Lactate Dehydrogenase, LDL, Total Cholesterol, Triglycerides, Amylase, Lipase
- Thyroid Function Tests: Thyroid Stimulation Hormone (TSH), Free T3 and Free T4
- Urine Pregnancy Test (HCG)
- Urine Analysis: pH (quantitative value only), Red Blood Cells, White Blood Cells, Protein, Glucose

Presentations will use SI Units. Unit conversions will be performed by Data Manager in the database where necessary.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of abnormal values according to normal range criteria
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements)
- Shift from baseline according to Common Toxicity (CTC) grading system (for measurements applicable based on Common Terminology Criteria for Adverse Events (CTCAE) v5.0)

15.3.1. Laboratory Specific Derivations

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units 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

15.3.2. CTC Grading for Laboratory Data

Hematology and Biochemistry laboratory quantitative parameters will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria (see Appendix 3), where applicable, and shift from baseline based on the classification will be presented.

15.4. 12-Lead Electrocardiogram (ECG) Evaluations

ECG data collected in 12-Lead ECG eCRF page will be included in the reporting of this study.

The following ECG parameters will be reported for this study, change from baseline will be prepared for quantitative parameters and summary by each visit will be display for qualitative parameter. The overall result of ECG shift from baseline to maximal on-treatment value during the on-treatment period will be summarized by cohort.

- Heart Rate (bpm)
- PR Interval (msec)
- RR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF (msec) [derived]
- Overall Result of ECG (Investigator's judgment):
  - Normal
  - Abnormal, Not Clinically Significant (ANCS)
  - Abnormal, Clinically Significant (ACS)
  - Unevaluable

15.4.1. 12-Lead Electrocardiogram (ECG) Specific Derivations

- Fridericia's Correction (msec)

$$QTcF\ (\text{msec}) = \frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$$

15.5. Immunogenicity Assessments

Blood samples for anti-drug antibody (ADA) analyses will be collected at predose in Cycle 1 and Cycle 2 and then in every other subsequent cycle, and at the mandatory Safety Follow-up Visit or until start of a new anti-cancer therapy, whichever occurs first. All samples will first be analyzed for ADAs in a screening assay. Study samples with results below the screening cut-off will be reported as negative for ADAs. In the event of a positive result in the screening assay, samples will be analyzed in the confirmatory assay. All samples confirmed positive will be reported as positive and will be further analyzed for presence of neutralizing antibodies (NAb).

The incidence of ADA will be summarized for all subjects who received at least one administration of investigational drug.

The immunogenicity results will be listed for ADA and NAb for each patient and time point.

15.5.1. Immunogenicity Assessments Specific Derivations

- Treatment-induced ADA: defined as any post-treatment positive ADA assay response when

the baseline ADA result is negative.

- Treatment-boosted ADA: defined as any post-treatment positive ADA assay response that is greater than or equal to 4-fold over baseline titer level when baseline is ADA positive in the ADA assay.
- ADA Incidence: sum of both treatment-induced and treatment-boosted

15.6. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Height (cm)
- Weight (kg)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Respiratory Rate (resp/min)
- Pulse Rate (bpm)
- Temperature (F)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Incidence of abnormalities: Normal/Abnormal

15.6.1. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Vital Signs	Markedly Abnormal Criteria	Note
HR	≤50 bpm and decrease from baseline ≥20 bpm	To be applied for all positions (including missing) except STANDING.
	≥120 bpm and increase from baseline≥20 bpm	
SBP	≤95 mmHg and decrease from baseline ≥20mmHg	To be applied for all positions (including missing) except STANDING.
	≥160 mmHg and increase from baseline ≥20 mmHg	
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
	≥110 mmHg and increase from baseline ≥10 mmHg	
Weight	≥5% increase from baseline	FDA Feb 2007.

15.7. PHYSICAL EXAMINATION

The following physical examination parameters will be reported for this study:

- General Conditions
- Respiratory System
- Cardiovascular System
- Abdomen
- Skin and Mucous Membranes
    - Head and Neck (including Eyes, Ears, Nose and Throat)
    - Thyroid
    - Lymph Nodes
    - Genitourinary System
    - Muscles and Bones (including Spine and Limbs)
    - Nervous System

The following summaries will be provided for physical examination data:

- Incidence of abnormalities: Normal/Abnormal, Not Clinically Significant (ANCS)/Abnormal, Clinically Significant (ACS)

15.8. ECOG PERFORMANCE STATUS

The following summaries of ECOG Performance Status will be reported for this study:

- 0
- 1
- 2
- 3
- 4
- 5

The ECOG shift from baseline to highest score during the on-treatment period will be summarized by cohort.

References

Protocol - CIBI308A102 Version 6, 7Jan2019

CRF - CIBI308A102 Version 03.00, 13Mar2019

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

The following conventions will be applied for reporting descriptive statistics of all continuous data:

- Mean, Median, Q1, Q3, Minimum, and Maximum will have the one more digit than RAW/SDTM data for non-derived data (e.g. weight).
- SD will be presented with one digit more than mean.
- Statistics on derived data (e.g. treatment exposure time in days) will be rounded to reasonable number of digits. Maximal digits should be available in ADaM datasets.

Outputs will be presented according to the following Global Bios > Processes > GBIOS Processes - Implementation Guidelines and Templates > General Guidelines and Templates > Output Conventions.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TIMEPOINTS

For outputs, treatment cycles will be represented as follows and in the order shown. Visits will be displayed as carried in the raw data, unless otherwise specified in the analysis dataset specifications. The number of visits and cycles will vary across subjects.

Long Name	Short Name (default for presentations)
Cycle x Day y	CxDy
Example: Cycle 1 Day 1 Cycle 2 Day 1 Cycle 2 Day 1 – Unscheduled 01	Example: C1D1 C2D1 C2D1 UNS01

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If study med start date ≤ AE start date ≤ the later of (study med stop +30 days or the safety follow-up visit), then TEAE If the later of (study med stop +30 days or the safety follow-up visit) < AE start date, then not TEAE
	Partial	If start date < study med start date, then not TEAE If study med start date ≤ AE start date ≤ the later of (study med stop +30 days or the safety follow-up visit), then TEAE If the later of (study med stop +30 days or the safety follow-up visit) < AE start date, then not TEAE
	Missing	If start date < study med start date, then not TEAE If study med start date ≤ AE start date ≤ the later of (study med stop +30 days or the safety follow-up visit), then TEAE If the later of (study med stop +30 days or the safety follow-up visit) < AE start date, then not TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If study med start ≤ AE stop date ≤ the later of (study med

START DATE	STOP DATE	ACTION
		stop +30 days or safety follow-up visit), then TEAE If the later of (study med stop +30 days or safety follow-up visit) < AE stop date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If study med start ≤ AE stop date ≤ the later of (study med stop +30 days or the safety follow-up visit), then TEAE If the later of (study med stop +30 days or the safety follow-up visit) < AE stop date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If study med start ≤ AE stop date ≤ later of (study med stop +30 days or the safety follow-up visit date), then TEAE If the later of (study med stop +30 days or safety follow-up visit date) < AE stop date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If study med start ≤ AE stop date ≤ the later of (study med stop +30 days or safety follow-up visit date), then TEAE If the later of (study med stop +30 days or safety follow-up visit date) < AE stop date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 3. **NCI CTCAE V5.0 LAB GRADES**

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Albumin (hypalbuminaemia)	g/L	[30, LLN)	[20, 30)	[0, 20)	
Alkaline Phosphatase increased	IU/L	(ULN, 2.5*ULN] if baseline is normal; [2*BL, 2.5*BL] if baseline is abnormal	(2.5*ULN, 5*ULN] if baseline is abnormal; [2.5*BL, 5*BL] if baseline is abnormal	(5*ULN, 20*ULN] if baseline is abnormal; [5*BL, 20*BL] if baseline is abnormal	>20*ULN if baseline is abnormal; >20*BL if baseline is abnormal
ALT (Alanine Aminotransferase) increased	IU/L	(ULN, 3*ULN] if baseline is normal; [1.5*BL, 3*BL] if baseline is abnormal	(3*ULN, 5*ULN] if baseline is abnormal; [3*BL, 5*BL] if baseline is abnormal	(5*ULN, 20*ULN] if baseline is abnormal; [5*BL, 20*BL] if baseline is abnormal	>20*ULN if baseline is abnormal; >20*BL if baseline is abnormal
AST (Aspartate Aminotransferase) increased	IU/L	(ULN, 3*ULN] if baseline is normal; [1.5*BL, 3*BL] if baseline is abnormal	(3*ULN, 5*ULN] if baseline is abnormal; [3*BL, 5*BL] if baseline is abnormal	(5*ULN, 20*ULN] if baseline is abnormal; [5*BL, 20*BL] if baseline is abnormal	>20*ULN if baseline is abnormal; >20*BL if baseline is abnormal
Blood Bilirubin increased	umol/L	(ULN, 1.5*ULN] if baseline is normal; [1*BL, 1.5*BL] if baseline is abnormal	(1.5*ULN, 3*ULN] if baseline is abnormal; [1.5*BL, 3*BL] if baseline is abnormal	(3*ULN, 10*ULN] if baseline is abnormal; [3*BL, 10*BL] if baseline is abnormal	>10*ULN if baseline is abnormal; >10*BL if baseline is abnormal
Cholesterol high	umol/L	(ULN, 7.75]	(7.75, 10.34]	(10.34, 12.92]	>12.92
Creatinine increased	umol/L	(ULN, 1.5*ULN]	(1.5*ULN, 3*ULN]; (1.5*BL, 3*BL]	(3*ULN, 6*ULN]; (3*BL, 6*BL]	>6*ULN
Glucose decreased (Hypoglycemia)	mmol/L	[3, LLN)	[2.2, 3)	[1.7, 2.2)	[0, 1.7)
Potassium increased (Hyperkalaemia)	mmol/L	(ULN, 5.5]	(5.5, 6]	(6, 7]	>7
Potassium decreased (Hypokalaemia)	mmol/L	[3, LLN)		[2.5, 3)	[0, 2.5)
Sodium increased (hypernatremia)	mmol/L	(ULN, 150]	(150, 155]	(155, 160]	>160
Hemoglobin decreased	g/L	[100, LLN)	[80, 100)	<80	
Hemoglobin increased	g/L	Increase in >0 - 20 g/L above ULN or above baseline if baseline is above ULN	Increase in >20 - 40 g/L above ULN or above baseline if baseline is above ULN	Increase in >40 g/L above ULN or above baseline if baseline is above ULN	-
Platelet decreased	10^9/L	[75, LLN)	[50, 75)	[25, 50)	[0, 25)
WBC decreased	10^9/L	[3, LLN)	[2, 3)	[1, 2)	[0, 1)
Leukocytosis	10^9/L	-	-	>100	
Lymphocytes decreased	10^9/L	[0.8, LLN)	[0.5 - 0.8)	[0.2 - 0.5)	[0, 0.2)
Lymphocyte increased	10^9/L	-	(4, 20]	>20	-
Neutrophil decreased	10^9/L	[1.5, LLN)	[1, 1.5)	[0.5, 1)	[0, 0.5)

- Grade 0: if Value is not missing and >= Normal Range Lower Limit [Decreased]; if Value is not missing and <= Normal Range Upper Limit [Increased]
- LLN=Lower Limit of Normal; ULN=Upper Limit of Normal; BL=Baseline
- Qualitative criteria will be ignored