Statistical Analysis Plan

Protocol: JTX-2011-R01

An Open-label, Multi-center, Rollover Study in Subjects with Advanced Solid Tumor Malignancies After Participation in a Vopratelimab (JTX-2011) Clinical Study

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SIGNATURE PAGE

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, which authorizes that the content is acceptable based on the current planned protocol.

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ABBREVIATIONS

AE	Adverse event
CR	Complete Response
CRF	Case Report Form
DOR	Duration of Response
ECGs	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
irAEs	Immune related adverse events
IRRs	Infusion related reactions
MedDRA	Medical Dictionary for Regulatory Activities
NE	Non-evaluable
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software

SOC	System Organ Class
SD	Stable Disease
TEAE	treatment-emergent adverse events

TRADEMARK INFORMATION

SAS	SAS (Statistical Analysis Software) is a registered trademark of SAS Institute Inc.

1. INTRODUCTION

This document describes the details of statistical analysis methodology for protocol JTX-2011-R01 (2.0, 03 August 2021), An Open-label, Multi-center, Rollover Study in Subjects with Advanced Solid Tumor Malignancies After Participation in a Vopratelimab (JTX-2011) Clinical Study. As background information, an overview of the study design is provided. Details of the summary and listings to be done are outlined in this document. Note: in this document any text taken directly from the protocol is ***italicised***.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective is to evaluate the long-term safety of continued treatment with vopratelimab monotherapy or combination treatment.

2.2 SECONDARY OBJECTIVES

The secondary objective is to evaluate the progression free survival (PFS) in subjects treated with vopratelimab monotherapy or combination therapy.

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives are as follows:

- *Examine changes from baseline in parent protocol in pharmacodynamic biomarkers including but not limited to phenotypes of immune cell subsets after treatment with vopratelimab monotherapy or vopratelimab in combination with nivolumab or in sequence with ipilimumab.*
- *Examine the correlation between pharmacodynamic biomarkers and duration of response and PFS.*

3. STUDY ENDPOINTS

3.1 PRIMARY ENDPOINT

- Incidence and severity of treatment-emergent adverse events (TEAEs), serious TEAEs, and discontinuation due to adverse events (AEs)evaluated using National Cancer Institute (NCI) Common Technology Criteria for Adverse Events (CTCAE) version 5.0 and death

3.2 SECONDARY ENDPOINTS

- Progression free survival (PFS), duration of response (DOR) as per RECIST version 1.1 and overall survival (OS)

3.3 EXPLORATORY ENDPOINTS

- Changes from baseline in parent protocol in pharmacodynamic biomarkers including but not limited to phenotypes of immune cell subsets after treatment with

vopratelimab monotherapy or vopratelimab in combination with nivolumab or in sequence with ipilimumab.

4. STUDY DESIGN

This is a rollover study that is designed to provide continued access to vopratelimab for eligible subjects with advanced solid tumor malignancies who have previously participated in a vopratelimab study (the parent study) after closure of the parent study.

Eligible subjects must have tolerated vopratelimab in the parent study without significant toxicities that otherwise would preclude further dosing in the opinion of the Investigator and/or Sponsor. Subjects must also be expected to receive continued benefit from treatment with vopratelimab in the opinion of the Investigator and/or Sponsor.

Subjects will continue to receive vopratelimab at the same dose and schedule received in the parent study, and ideally will experience no treatment interruption between the end of participation in the parent study and entry into the rollover study. Any changes to the dose and schedule of vopratelimab must be in accordance with a dose and schedule previously shown to be safe and well tolerated and must be discussed with the medical monitor. Subjects who received combination treatment on the parent study will also continue to receive the partner drug (e.g., nivolumab or ipilimumab) at the same dose and schedule as in the parent study. Any changes to the dose and schedule of nivolumab or ipilimumab must be discussed with the medical monitor.

Safety will be evaluated continuously for the duration of a subject's participation. Imaging for disease status will be performed in accordance with institutional standard of care guidelines and must be performed at least every 6 months (± 3 weeks).

All subjects must sign a new informed consent form to be enrolled in the rollover study. Subjects may continue to receive study treatment until loss of clinical benefit or unacceptable toxicity as defined by the Investigator and/or Sponsor, withdrawal of consent, loss to follow-up, or death.

4.1 TREATMENT ASSIGNMENT AND BLINDING

Treatment Assignment

There is no new treatment assignment in the rollover study. Patients in rollover study will continue to receive vopratelimab and any partner drugs administered in the parent study (e.g., nivolumab, ipilimumab).

Blinding

The study is not blinded.

5. SAMPLE SIZE CONSIDERATION

Not appliable. Patients on study treatment in a Jounce-sponsored clinical study and eligible for rollover may be enrolled. For the study objectives, no prospective sample size determination is required.

6. STATISTICAL METHODS

6.1 GENERAL CONSIDERATIONS

Individual subject listings will be presented for data collected for rollover study. Data listings will be sorted by parent study id, subject number and date collected where applicable.

Table summary may be provided as appropriate. Categorical data will be summarized by frequency distribution (number and percentage of subjects falling within each category). Continuous variables will be summarized by descriptive statistics including N, mean, standard deviation, median, and range (minimum and maximum).

Data analyses will be conducted using the SAS® System (SAS Institute, Inc., Cary, NC, USA) Version 9.4 or above.

6.1.1 BASELINE

Baseline for subjects in the rollover study is defined as the baseline in the parent study.

For deriving time-to-event efficacy endpoints (PFS, OS, DOR), starting date from parent study will be used with details as follows:

- PFS/OS will be calculated from date of the first dose study drug from parent study.
- DOR will be calculated from date of first confirmed response from parent study.

6.2 ANALYSIS POPULATIONS

Enrolled subjects will include all subjects who have signed the ICF for rollover study.

The Safety Population (SAF) will include all subjects who have been treated with at least one dose of study drug in the rollover study.

6.3 TREATMENT MISALLOCATIONS

Not applicable.

6.4 STUDY SUBJECTS

6.4.1 SUBJECT DISPOSITION AND COMPLETION STATUS

Subject disposition summary will be provided for all subjects categorized by parent study. The summary will include subjects treated, disposition of subjects with respect to treatment discontinuation and end of study status for the rollover study including reasons for treatment discontinuation and study exit will be provided. Deaths within 30 days of last dose and death beyond 30 days of last dose will be summarized separately along with primary cause of death.

Subject disposition listing will also be provided.

6.4.2 DEMOGRAPHICS , BASELINE CHARACTERISTICS

Subject listing for demographics and baseline disease characteristics will be provided.

6.4.3 STUDY DRUG EXPOSURE

Individual listing for study drug administration will be provided for vopratelimab and any partner drugs administered in the parent study (e.g., nivolumab, ipilimumab) for each dose administration with information regarding intended dose/actual dose, dose modification (and reason if any).

Duration of exposure (days) in rollover study will be defined for each subject and also separately for each study drug as follows:

Duration on study drug X (days)= last dose date of study drug X in rollover study– first dose date of study drug X in rollover study +1

Duration on treatment (days)=max(last dose date of each study drug in rollover study) – min(first dose date of each study drug in rollover study) +1

In addition, overall duration of exposure (overall duration of each study drug and duration of treatment) will also be calculated similarly as above counting from first dose in parent study.

Number of treatment cycles in rollover study and total number of treatment cycles (including parent study and rollover study) will be derived for each subject.

For each study drug, cumulative dose received in rollover study and total cumulative dose received (including parent study and rollover study) will be calculated for each subject.

Duration of exposure (in rollover study and overall), number of treatment cycles (in rollover study and total), cumulative dose received cycles (in rollover study and total) will be provided in data listings.

6.4.4 CONCOMITANT MEDICATIONS

Individual listings will be provided for concomitant medications. Concomitant medications will be coded by WHO Drug Dictionary. Concomitant medications will include all concomitant medications taken on or after the date of first dose of study drug or any concomitant medication started prior to first dose of study drug that continued beyond the date of first dose of study drug in rollover study.

6.4.5 MEDICAL HISTORY

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary v23.0 or higher and will be listed.

6.5 EFFICACY ANALYSES

The efficacy endpoints include progression-free survival (PFS), duration of response (DOR) and overall survival (OS), all relative to C1D1 of the parent study.

6.5.1 PROGRESSION-FREE SURVIVAL

Progression-free survival (PFS) is defined as the time from the first dose of study drug from parent study until the first documentation of a disease progression or death due to any cause, whichever occurs first regardless of whether the subject receives subsequent anticancer therapy prior to progression. Patients who have no documented progression and are still alive at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. PFS is defined in months as follows:

PFS (months) = (Date of PD/death or censoring – Date of the first dose study drug from parent study + 1) / (365.25/12)

Individual subject listing will be provided for PFS including PFS time, event/censor date and event/censoring description.

6.5.2 DURATION OF RESPONSE

Duration of response (DOR) is defined as the time from the first documentation of a subsequently confirmed objective response from parent study until the first documentation of disease progression or death due to any cause, whichever occurs first regardless of whether the subject receives subsequent anticancer therapy prior to progression. For subjects who are alive and progression-free at the time of data cut-off for analysis, DOR will be censored at the last tumor assessment date. Only subjects who have achieved objective response (confirmed CR or confirmed PR) will be evaluated for DOR. DOR is defined in months as follows:

DOR (months) = (Date of PD/death or censoring – Date of first confirmed response from parent study + 1) / (365.25/12),

The date of PD/death or censoring is the same as defined for PFS.

Individual subject listing will be provided including DOR, BOR, start date of response, event/censoring date and event/censoring description. Start date of subsequent anticancer therapy will be also be included when applicable.

6.5.3 OVERALL SURVIVAL

Overall survival (OS) is defined as the time from the first dose of study product from parent study until death due to any cause. For patients who are alive at the time of analysis, OS will be censored on the last date when patients are known to be alive.

OS is defined in months as follows:

OS (months) = (Date of death or censoring – Date of the first dose of study drug from parent study + 1) / (365.25/12).

Individual subject listing will be provided.

6.6 SAFETY ANALYSES

The safety listings will include the evaluation of the following data:

- Adverse events (AEs)
- Laboratory results
- Vital signs: pulse rate, respiration rate, temperature, systolic and diastolic blood pressure, and weight
- Electrocardiograms (ECGs)
- Physical exams
- ECOG Status

The SAF will be used for displaying safety outputs unless otherwise specified. Data will be provided in subject listings.

6.6.1 ADVERSE EVENTS

6.6.1.1 ADVERSE EVENT DEFINITIONS

Adverse events will be coded into standardized terminology according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary v23.0 or higher. Severity of AE will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE, v5.0).

- Treatment-Emergent Adverse Events (TEAEs) are designated as events that occur after the start of study drug(s), and were not observed prior to start of treatment; Or if the event was observed prior to the start of study drug but worsened after the start of study drug in the rollover study.

- Treatment Related TEAEs will include those TEAEs which are considered related to study drugs as designated by the investigator and/or Sponsor.

- Serious adverse events (SAEs) will include all events classified as serious on the eCRF. The electronic database used to enter data at the site will be deemed as the source of record for adverse event information. The safety and pharmacovigilance database will be reconciled against the EDC.

- Immune-related adverse events (irAEs) are unique side effects typically seen after dosing with checkpoint inhibitors and are derived based on eCRF irAE flag. Some of the most common irAEs include: pneumonitis, colitis, hepatitis, endocrinopathy , adrenal insufficiency, hypothyroidism and hyperthyroidism, , nephritis, dermatitis, and neuropathy Summary of Adverse Events

6.6.1.2 SUMMARY OF ADVERSE EVENTS

Adverse events (AEs) will be listed. Listings will be created by categories for AEs as outlined below:

- All adverse events (AEs) with flags for treatment emergent adverse events (TEAEs) and flags of relatedness to study drug(s)
- SAEs with flags for treatment emergent adverse events (TEAEs) and flags of relatedness to study drug(s)
- Immune related adverse events (irAEs)
- Infusion related reactions (IRRs)
- TEAEs leading to death
- TEAEs leading to study drug interruption, reduction, hold or permanent study drug discontinuation

A general overview summary table will also be provided include frequencies by category of AE (as listed above) and will also include TEAE by severity grade and relationship to study drugs.

6.6.2 LABORATORY DATA

Laboratory data will be listed separately for hematology, chemistry, coagulation and urinalysis panels with lab results, normal ranges, CTCAE grade (as applicable).

6.6.3 VITAL SIGNS AND ECG

Individual data listings will be provided for vital sign parameters: systolic and diastolic blood pressure (mmHg), respiratory rate (breaths per minute), body temperature (C°), weight (kg) and pulse rate (beats per minute).

TABLE 1 NORMAL RANGE OF VITAL SIGNS

Parameter	Units	Normal Range
Systolic Blood Pressure	mmHg	90 - 120
Diastolic Blood Pressure	mmHg	60 - 80
Pulse Rate	Beats per minute	60-100
Respiratory Rate	Breaths per minute	12 – 20
Temperature	◦C	36.1 – 37.2

6.6.4 ELECTROCARDIOGRAM (ECG)

Individual data listings will be provided, including observed and change from baseline values will be presented for ECG measures of PR interval, QRS duration, QT interval, QTc interval and overall interpretation.

6.6.5 PHYSICAL EXAMS

Physical exam data will be presented in a data listing.

6.6.6 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

The Eastern Cooperative Oncology Group (ECOG) performance status data will be presented in subject listings.

6.7 EXPLORATORY BIOMARKER ANALYSIS

Exploratory pharmacodynamic biomarkers collected in rollover studies will be listed when available.

There is no additional analysis planned for exploratory biomarkers for this study..

7. INTERIM ANALYSIS

Not applicable.

8. REFERENCES

E. A. Eisenhauer, P. Therasse, J. Bogaerts, L. H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, and J. Verweij, New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 2009. 45(2): p. 228-47.

FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics. April 2015.

9. VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	01Dec2022	Initial document	Initial document