# Statistical Analysis Plan

NCT Number: NCT06390995

Title: A phase 1/2 open-label study to evaluate the safety, tolerability, efficacy and pharmacokinetics of mirvetuximab soravtansine (TAK-853) in Japanese patients with folate receptor alpha-positive advanced ovarian cancer and other solid tumors

Study Number: TAK-853-1501
Document Version and Date: Version 2.0 / 29-MAY-2025

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

# STATISTICAL ANALYSIS PLAN

Study Number: TAK-853-1501

Study Title: A phase 1/2 open-label study to evaluate the safety, tolerability, efficacy and pharmacokinetics of mirvetuximab soravtansine (TAK-853) in Japanese patients with folate receptor alpha-positive advanced ovarian cancer and other solid tumors

Phase: 1/2

Version: 2.0

Date: 29 May 2025

Prepared by: [redacted]

Based on:

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Protocol Date: 12 June 2024

## REVISION HISTORY

| Version | Approval Dat | Primary Rationale for Revision |
|---|---|---|
| version 1.0 | 19-Apr-2024 | Protocol updated |
| | | |

## TABLE OF CONTENTS

## ABBREVIATIONS

| | |
|---|---|
| ADA | Anti-drug antibodies |
| AE | adverse event |
| AECI | adverse event of clinical interest |
| AIBW | adjusted ideal body weight |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BCVA | best corrected visual acuity |
| BOR | Best overall response |
| BRCA | Breast cancer susceptibility gene |
| CI | confidence interval |
| CR | complete response |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| eCRF | electronic case report form |
| EOS | end of study |
| EOT | end of treatment |
| FAS | full analysis set |
| FRα | folate receptor α |
| IV | intravenous |
| KM | Kaplan-Meier |
| MIRV | mirvetuximab soravtansine |
| MTD | maximum tolerated dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NE | not evaluable |
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PDS | Programming Derivation Specification |
| PFS | progression free survival |
| PK | pharmacokinetic |
| PLD | Pegylated liposomal doxorubicin |
| PR | partial response |
| PROC | platinum-resistant ovarian cancer |
| PT | Preferred term |
| Q3W | once every 3 weeks |
| RECIST | Response Evaluation Criteria in Solid Tumors |

| | |
|---|---|
| RP2D | recommended phase 2 dose |
| SAE | serious adverse event |
| SD | stable disease |
| SOC | System Organ Class |
| TEAE | treatment-emergent adverse event |
| ULN | Upper limit of normal |
| WHO | World Health Organization |

# 1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

## 1.1 Objectives

### 1.1.1 Primary Objective

**Phase 1 part**

*To evaluate the safety and tolerability of Mirvetuximab Soravtansine (MIRV) at 6.0 mg/kg adjusted ideal body weight (AIBW) when administered IV Q3W in Japanese patients with folate receptor alpha (FRα)-positive advanced ovarian cancer or other solid tumors.*

**Phase 2 part**

*To determine the efficacy of MIRV in patients with platinum-resistant ovarian cancer (PROC) and high FRα expression.*

### 1.1.2 Secondary Objective(s)

**Phase 1 part**

- *To characterize the pharmacokinetics of MIRV.*
- *To characterize the immunogenicity of MIRV.*

**Phase 2 part**

- *To determine the durability of response to MIRV based on investigator assessment.*
- *To evaluate the safety profile of MIRV when administered IV.*
- *To characterize the pharmacokinetics of MIRV.*
- *To characterize the immunogenicity of MIRV.*

[redacted]

## 1.2 Endpoints

### 1.2.1 Primary Endpoint(s)

***Phase 1 part***

*The Phase 1 primary endpoints are:*

- *The number and percentage of patients with DLTs in Cycle 1.*
- *AEs including:*
  - *The number and percentage of patients with TEAEs.*
  - *The number and percentage of patients with Grade 3 or higher TEAEs.*
  - *The number and percentage of patients with serious TEAEs.*
  - *The number and percentage of patients with TEAEs leading to drug discontinuation.*
  - *The number and percentage of patients with TEAEs leading to infusion interrupted.*
  - *The number and percentage of patients by Preferred Term of TEAEs leading to dose delayed.*
  - *The number and percentage of patients with TEAEs leading to dose reduction.*
  - *The number and percentage of patients with AEs of clinical interest (AECIs).*

***Phase 2 part***

*The Phase 2 primary endpoint is objective response rate (ORR) based on the investigator's assessment using RECIST v1.1.*

### 1.2.2 Secondary Endpoint(s)

**Phase 1 part**

*The Phase 1 secondary endpoints are:*

- *PK parameters for intact ADC, total Ab, DM4 and S-methyl DM4: maximum observed plasma concentration ($C_{max}$), area under the plasma concentration-time curve (AUC), terminal half-life ($t_{½}$), total clearance (CL), volume of distribution at steady state ($V_{ss}$), time of first occurrence of $C_{max}$ ($t_{max}$) as applicable.*
- *Incidence of immunogenicity of MIRV.*

**Phase 2 part**

- *Duration of response (DOR) based on the investigator's assessment, defined as the time from the first assessment of either CR or PR until progressive disease.*
- *Intact ADC, total Ab, DM4 and S-methyl DM4 concentration.*

- *Incidence of immunogenicity of MIRV.*

[redacted]

### 1.2.4 Safety Endpoints

**Phase 2 part**

- *Adverse events including:*
  - *The number and percentage of patients with TEAEs after study drug administration.*
  - *The number and percentage of patients with Grade 3 or higher TEAEs.*
  - *The number and percentage of patients with serious TEAEs.*
  - *The number and percentage of patients with TEAEs leading to drug discontinuation.*
  - *The number and percentage of patients with TEAEs leading to infusion interrupted.*
  - *The number and percentage of patients with TEAEs leading to dose delayed.*
  - *The number and percentage of patients with TEAEs leading to dose reduction.*
  - *The number and percentage of patients with AECIs.*
- *Laboratory values*
- *Vital signs*

### 1.3 Estimand(s)

Not applicable.

## 2.0 STUDY DESIGN

*This is a Phase 1/2 study. Initially, the study will start as a Phase 1 study to assess the safety of the global recommended phase 2 dose (RP2D) of Mirvetuximab Soravtansine (MIRV, TAK-853) 6.0 mg/kg AIBW when administered intravenously Q3W in Japanese patients with FRα-positive advanced ovarian cancer or other solid tumors. After it is confirmed that the RP2D in Japanese patients is safe, a Phase 2 part will be followed; the Phase 2 part is designed to evaluate the efficacy and safety of MIRV in patients with PROC and high FRα expression. This study will be conducted under open-label in Japan. Eligible patients, who have provided informed consent and meet study entry criteria will be enrolled in the study.*

*Disease progression will be evaluated by the Investigator using Response Evaluation Criteria In Solid Tumors RECIST v 1.1.*

*Patients will continue to receive study drug until disease progression, unacceptable toxicity, withdrawal of consent, death, or until the Sponsor terminates the study (whichever comes first).*

*Tumor assessments, including radiological assessments by CT/MRI scans will be performed at Screening and subsequently every 6 weeks (± 1 week) from C1D1 for the first 36 weeks then every 12 weeks (± 3 weeks) until disease progression, death, the initiation of subsequent anticancer therapy, or patient's withdrawal of consent, whichever occurs first.*

*For phase 1 part, if patients discontinue study treatment for reasons other than progressive disease (PD), a tumor assessment is to be performed at the End of Study visit or 30-day Follow up visit, if not performed within the previous 6 weeks. Additional tumor assessments may be conducted based on the investigator's decision.*

*For phase 2 part, patients who discontinue study treatment for reasons other than PD will continue with tumor assessments until documentation of PD or the start of a new anticancer therapy, whichever comes first.*

*For phase 2 part, all patients who discontinue study drug will be followed every 3 months (± 1 month) until death, lost to follow-up, withdrawal of consent for survival follow-up, or end of study (EOS), whichever comes first.*

*Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, with exception of corneal adverse events which will be also evaluated according to non-CTCAE grading as defined in the protocol.*

## 3.0 STATISTICAL HYPOTHESES AND DECISION RULES

### 3.1 Statistical Hypotheses

Not applicable.

### 3.2 Statistical Decision Rules

Not applicable.

### 3.3 Multiplicity Adjustment

Not applicable.

## 4.0 SAMPLE-SIZE DETERMINATION

Phase 1 part

*The study will follow a 3+3+3 design. 6.0 mg/kg AIBW is the only dose level to be evaluated in this trial. Patients will be enrolled and treated at the dose level 6.0 mg/kg AIBW with 3 patients in each cohort. The number of evaluable patients is planned to be 3 to 9.*

Phase 2 part

*Approximately 22 patients will be enrolled and a total of 20 patients will be evaluated for efficacy analysis, assuming a dropout rate of 10%. This will allow the study to have over 80% power to detect a difference in ORR of 26% (42% vs 16%) with a 1-sided alpha of 0.05. These results assume that the ORR is 16% under the null hypothesis and 42% under the alternative hypothesis.*

## 5.0 ANALYSIS SETS

**Phase 1 Part**

- *Safety analysis set*

  *The safety population is defined as all patients who receive at least 1 dose of MIRV. The safety analysis set will be used for safety analysis.*

- *PK analysis set*

  *The PK analysis set is defined as all patients for whom there are sufficient dosing and MIRV concentration-time data to reliably estimate the PK parameter(s). This population will be used for analyses of PK parameters and population PK analyses.*

- *Response-Evaluable Population*

  *The response-evaluable population is defined as patients who have radiographic assessment at baseline, receive at least 1 dose of MIRV, and have at least 1 post-baseline tumor assessment or died or clinically progressed within 105 days of last dose. The response-evaluable population will be used for efficacy analysis.*

[redacted]

**Phase 2 Part**

- *Full analysis set*

  *All patients who receive at least 1 dose of MIRV. The full analysis set will be used for efficacy analysis.*

- *Safety analysis set*

  *The safety population is defined as all patients who receive at least 1 dose of MIRV. The safety analysis set will be used for safety analysis.*

- *PK analysis set*

  *The PK analysis set is defined as patients who receive at least 1 dose of MIRV and have at least 1 plasma concentration data after administration of MIRV. This population will be used for PK analyses and population PK analyses.*

[redacted]

## 6.0 STATISTICAL ANALYSIS

### 6.1 General Considerations

Baseline values are defined as the last observed value before the first dose of study medication.

For confidence interval (CI), unless otherwise specified, the 95% confidence interval will be presented.

Unless otherwise specified, the categories of any undefined categorical analysis variables are determined by the codelist labels of the eCRF.

Technical details such as the derivation of complex endpoints and analysis variables, complex (e.g. non-standard) algorithms related to the handling of missing data, visit windowing, criteria for markedly abnormal values, data handling conventions to handle missing or partial dates or statistical analysis code will be not included in this statistical analysis plan. The technical details will be captured in a programming derivation specification (PDS).

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

#### 6.1.1 Analysis Approach for Continuous Variables

Continuous variables will be summarized using the descriptive statistics (N, mean, median, standard deviation (SD), minimum, and maximum) unless stated otherwise.

### 6.1.2 Analysis Approach for Binary Variables

All binary variables will be presented with the number and percent per category unless stated otherwise in the section specific to an endpoint.

### 6.1.3 Analysis Approach for Time-to-Event Variables

All time-to-event variables in this study will use the analysis method below unless stated otherwise in the section specific to an endpoint.

For time-to-event variables such as duration of response (DOR), progression-free survival (PFS) and overall survival (OS), the analysis method below will be used unless stated otherwise in the section specific to an endpoint.

Breakdown of the number of subjects who were censored and who experienced an event will be summarized. Quartiles of time to event with associated 2-sided 95% confidence intervals (CIs) will be estimated using the Kaplan-Meier method. Kaplan-Meier estimate of survival probability at specific time points will also be provided. The Kaplan-Meier plot will be presented.

## 6.2 Disposition of Subjects

### 6.2.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Date First Subject Signed Informed Consent Form

Date of Data Cutoff

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Methods:

(1) Study Information

Study information shown in the analysis variables section will be provided for Phase 1 and Phase 2 part.

### 6.2.2 Screen Failures

Analysis Set:

Subjects Who Were Screening Failure

Analysis Variables:

Age (years)

Sex [Male, Female]

Ethnicity [Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown]

Race [American Indian or Alaska Native, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, White, Not Reported]

Primary Reason for Screen Failures

[Adverse Event, Withdrawal by Subject, Pregnancy, Screen Failure (Did Not Meet Eligibility Criteria), Other]

Analytical Methods:

(1) Summary of Demographics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided for Phase 1 part and Phase 2 part.

### 6.2.3 Disposition of Subjects

Analysis Set:

Safety Analysis Set

Analysis Variables:

Status of the Treatment

[Still on Treatment, Discontinued Study Treatment]

Primary Reason for Discontinuation of Treatment

[Adverse Event, Protocol Deviation, Progressive Disease, Failure to Meet Continuation Criteria, Study Terminated by Sponsor, Withdrawal by Subject, Loss to Follow-up, Other]

Status of the Study (Phase 1)

[During the Response or Survival Follow Up, Permanently Discontinued from Study, Study Completed]

Status of the Study (Phase2)

[During the Response or Survival Follow Up, Permanently Discontinued from Study]

Primary Reason for Discontinuation of Study

[Loss to Follow-up, Study Terminated by Sponsor, Withdrawal by Subject, Death, Progressive Disease, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided for Phase 1 part and Phase 2 part. When calculating percentages of the reasons for discontinuation of study and treatment, the total number of subjects in the safety analysis set will be used as the denominator.

### 6.2.4 Protocol Deviations and Analysis Sets

*6.2.4.1 Protocol Deviations*

Analysis Set:

All Subjects Who Were Enrolled into Treatment Period

Analysis Variables:

Significant Protocol Deviation

Analytical Methods:

(1) Protocol Deviations

Frequency distribution will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once. The analysis will be provided for Phase 1 part and Phase 2 part.

*6.2.4.2 Analysis Sets*

Analysis Set:

All Subjects Who Were Enrolled into Treatment Period

Analysis Variables:

Handling of Subjects

[Categories are based on the specifications in Subject Evaluability List]

Analysis Sets

| | |
|---|---|
| Safety Analysis Set | [Included] |
| Full Analysis Set (Ph2 only) | [Included] |
| [redacted] | [redacted] |
| Response-Evaluable Population (Ph1 Only) | [Included] |
| PK Analysis Set | [Included] |

Analytical Methods:

(1) Analysis Sets

Frequency distributions will be provided for Phase 1 part and Phase 2 part.

## 6.3 Demographic and Other Baseline Characteristics

### 6.3.1 Demographics

Analysis Set:

Safety Analysis Set

Analysis Variables:

Age (years)

Age (group1) [18=< - <=64, 65<= - <=Max]

Age (group2) [18=< - <=64, 65<= - <=74, 75<= - <= 84, 85<= - <=Max]

Age (group3) [18=< - <=69, 70<=- <=Max]

Sex [Male, Female]

Ethnicity [Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown]

Race [American Indian or Alaska Native, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, White, Not Reported]

Race (Asian) [Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Not Reported]

Baseline Height (cm)

Baseline Weight (kg)

Baseline AIBW (kg)

Analytical Methods:

(1) Summary of Demographics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided for Phase 1 part and Phase 2 part.

### 6.3.2 Baseline Characteristics

Analysis Set:

Safety Analysis Set

Analysis Variables:

Primary Diagnosis

Any (BRCA) Mutations

[Positive, Negative, Unknown]

BRCA1 Positive

BRCA2 Positive

Histology

Time since Initial Diagnosis to Date of First Dose of Study Drug (months)

Stage at Initial Diagnosis

[Stage I - IIA, Stage IIB - IIC, Stage IIIA, Stage IIIB, Stage IIIC, Stage IV- IVD, Not Available, Other]

Histologic Grade

[Well Differentiated, Moderately Differentiated, Poorly Differentiated, Undifferentiated, Unknown]

Prior Radiation Therapy [Yes, No]

Number of Prior Lines of Therapy (Ph1 only) [1, 2, 3, 4+]

Number of Prior Lines of Therapy (Ph2 only) [1, 2, 3]

Best Response to the 1st Line

[Complete Response, Partial Response, Stable Disease, Progressive Disease, Not Evaluable, Unknown]

Best Response to the Last Line

[Complete Response, Partial Response, Stable Disease, Progressive Disease, Not Evaluable, Unknown]

Prior Cancer Related Surgery [Yes, No]

Prior Exposure to Platinum [Yes, No]

Prior Exposure to Bevacizumab [Yes, No]

Prior Exposure to PARP Inhibitors [Yes, No]

Prior Exposure to Taxanes [Yes, No]

Prior Exposure to Doxorubicin/PLD [Yes, No]

Prior Exposure to Topotecan [Yes, No]

Prior Exposure to Gemcitabine [Yes, No]

Prior Exposure to Kinase Inhibitor [Yes, No]

Prior Exposure to Hormonal Therapy [Yes, No]

Primary Platinum-free Interval (months) [≤12 months, >12 months, Missing]

Platinum-free Interval [≤3 months, >3 - ≤6 months, >6 months]

ECOG Performance Status [0, 1, 2, 3, 4, Missing]

FRα PS2+ Score (Ph2 only)

Analytical Methods:

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided for Phase 1 part and Phase 2 part.

### 6.3.3 Medical History

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medical History

Analytical Methods:

(1) Medical History by System Organ Class and Preferred Term

Frequency distributions will be provided for Phase 1 and Phase 2. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. A subject with multiple occurrences of medical history within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history within a PT will be counted only once in that PT.

## 6.4 Medication History and Concomitant Medications

### 6.4.1 Prior Anticancer Therapy

Analysis Set:

Safety Analysis Set

Analysis Variables:

Prior Anticancer Therapy

Analytical Methods:

(1) Prior Anticancer Therapy by Standardized Medication Name

Frequency distributions will be provided for Phase 1 and Phase 2 part. WHO Drug dictionary will be used for coding. Summaries will be provided using standardized medication name and sorted in decreasing frequency based on the number of reports. A

subject who has been administered several medications with the same standardized medication name will be counted only once for that standardized medication name.

### 6.4.2 Concomitant Medications

Concomitant medications are defined as medications which are taken during the study treatment and within 30 days of the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever occurs first.

Analysis Set:

Safety Analysis Set

Analysis Variables:

Concomitant Medications

Analytical Methods:

(1) Concomitant Medications by Standardized Medication Name

Frequency distributions will be provided for Phase 1 and Phase 2 part. WHO Drug dictionary will be used for coding. Summaries will be provided using standardized medication name and sorted in decreasing frequency based on the number of reports. A subject who has been administered several concomitant medications with the same standardized medication name will be counted only once for that standardized medication name.

### 6.4.3 Prior and Concomitant Procedures

Prior procedures are defined as occurring before the first dose of study drug (by procedure date). Concomitant procedures are defined as procedures with a procedure date on or after the first dose of study drug, and within 30 days of the last dose of study drug or prior to the start of subsequent anticancer therapy, whichever occurs first.

Analysis Set:

Safety Analysis Set

Analysis Variables:

Prior Procedures

Concomitant Procedures

Analytical Methods:

(1) Prior Procedures by System Organ Class and Preferred Term

(2) Concomitant Procedures by System Organ Class and Preferred Term

Frequency distributions will be provided for Phase 1 and Phase 2. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC

will be sorted alphabetically and PT will be sorted in decreasing frequency. A subject with multiple occurrences of prior or concomitant procedures within a SOC will be counted only once in that SOC. A subject with multiple occurrences of prior or concomitant procedures within a PT will be counted only once in that PT.

## 6.5 Efficacy Analysis

### 6.5.1 Primary Endpoint(s) Analysis

#### *6.5.1.1 Derivation of Endpoint(s)*

- Best overall response (BOR) for a patient is the best response recorded between the date of first infusion of the study drug and the date of objectively documented PD per RECIST Version 1.1, the date of the start of new anti-cancer therapy, or the date of study discontinuation, whichever occurs first. When an analysis cutoff date is implemented, only radiological assessments occurring on or prior to the cutoff date will be used for analysis. Patients with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks (28 days) after the criteria for response are first met. When stable disease is the best overall response, it must meet the minimum duration of 35 days (6 weeks – 1 week window = 35 days from the date of first dose). The confirmatory scan is valid following treatment discontinuation as long as the patient has not started a new anti-cancer therapy.
- ORR is defined as the proportion of patients who achieved a confirmed PR or confirmed CR during the study using RECIST version 1.1. For patients with an overall response of PR or CR at a given time point, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Patients without post-baseline RECIST assessment will be treated as non-responders.

#### *6.5.1.2 Main Analytical Approach*

Analysis Set:

Response-Evaluable Population

Full Analysis Set

Analysis Variables:

ORR assessed by the investigator

BOR assessed by the investigator

Analytical Methods:

(1) For ORR assessed by the investigator in Phase 1 part, point estimate and the 2-sided 95% exact CI based on the Clopper-Pearson interval method will be provided by using response-evaluable population. For ORR assessed by the investigator in Phase 2 part,

point estimate and the 2-sided 90% exact CI based on the Clopper-Pearson interval method will be provided by using full analysis set. BOR by investigator assessment will be summarized using the categories of CR, PR, SD, PD, NE.

(2) Waterfall plot

A waterfall plot of best percent change in sum of target lesion size from baseline will be presented for each phase.

(3) Swimmer plot

A swimmer plot of overall response will be presented for each phase.

*6.5.1.3 Subgroup Analyses*

Analysis Set:

Full Analysis Set

Analysis Variables:

ORR assessed by the investigator

Subgroups:

BRCA Status (BRCA1 and/or BRCA2 Positive, Negative/Unknown).

Age Group (< 65 years vs ≥65 years).

Prior Exposure to Bevacizumab (Yes vs NO).

Number of Prior Lines of Therapy (1 vs 2 vs 3 vs (1 or 2)).

Primary Platinum-free Interval (≤ 6 months vs >6 months).

Most Recent Platinum-free Interval (≤ 3 months vs >3 months).

Prior Exposure to PARPi Maintenance Therapy (Yes vs No).

Stage at Diagnosis (I-III vs IV).

Weight at Baseline (<60kg, ≥60kg).

Analytical Methods:

For ORR assessed by the investigator in Phase 2 part, point estimate and the 2-sided 90% exact CI based on the Clopper-Pearson interval method will be provided for each subgroup. Best overall response by investigator assessment will be summarized using the categories of CR, PR, SD, PD, NE.

### 6.5.2 Secondary Endpoint(s) Analysis

#### *6.5.2.1 Derivation of Endpoint(s)*

For patients with confirmed CR/PR per RESIST v1.1, DOR is defined as the time from the first observation of CR/PR (whichever is first recorded) to the first date at which progressive disease is objectively documented per RECIST v1.1, or death due to any cause, whichever occurs first. DOR will be expressed in month, i.e. DOR = (earliest date of progression or death – date of first CR/PR + 1) / 30.4375.

General censoring rules for DOR will be as follows:

- Subjects who receive new anti-cancer therapy prior to PD or death (including palliative radiotherapy during study treatment) will be censored on the date of last radiological assessment prior to the start of the new anticancer therapy.
- Subjects who experience PD or death after missing 2 or more consecutive radiological assessments will be censored on the date of last RECIST assessment.
- Subjects who experience no documented disease progression or death will be censored on the last radiological assessment.
- When an analysis cutoff date is implemented, only data (deaths and radiological assessments) occurring on or prior to the cutoff date will be used for analysis.

#### *6.5.2.2 Main Analytical Approach*

Analysis Set:

Full Analysis Set

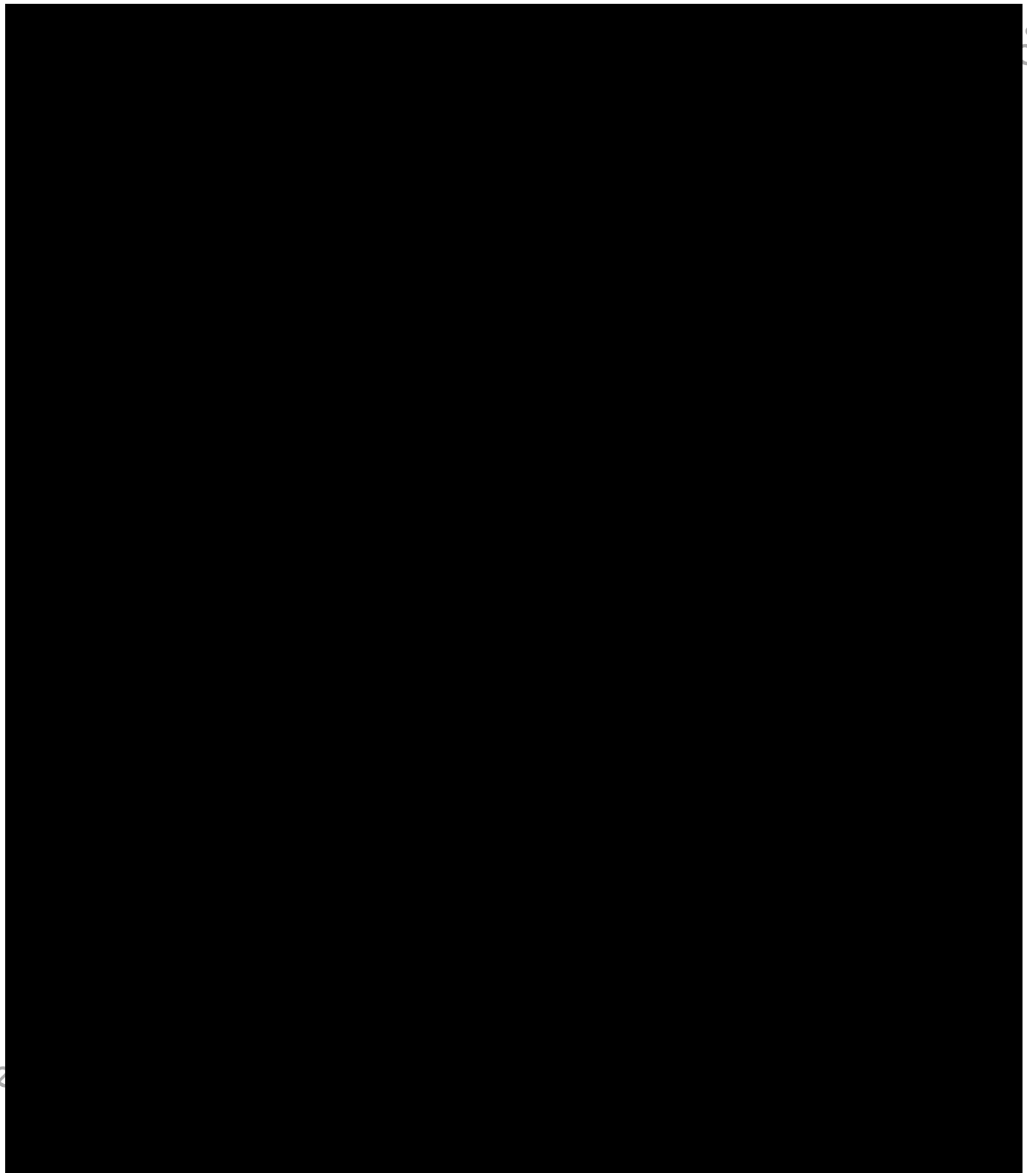
Analysis Variables:

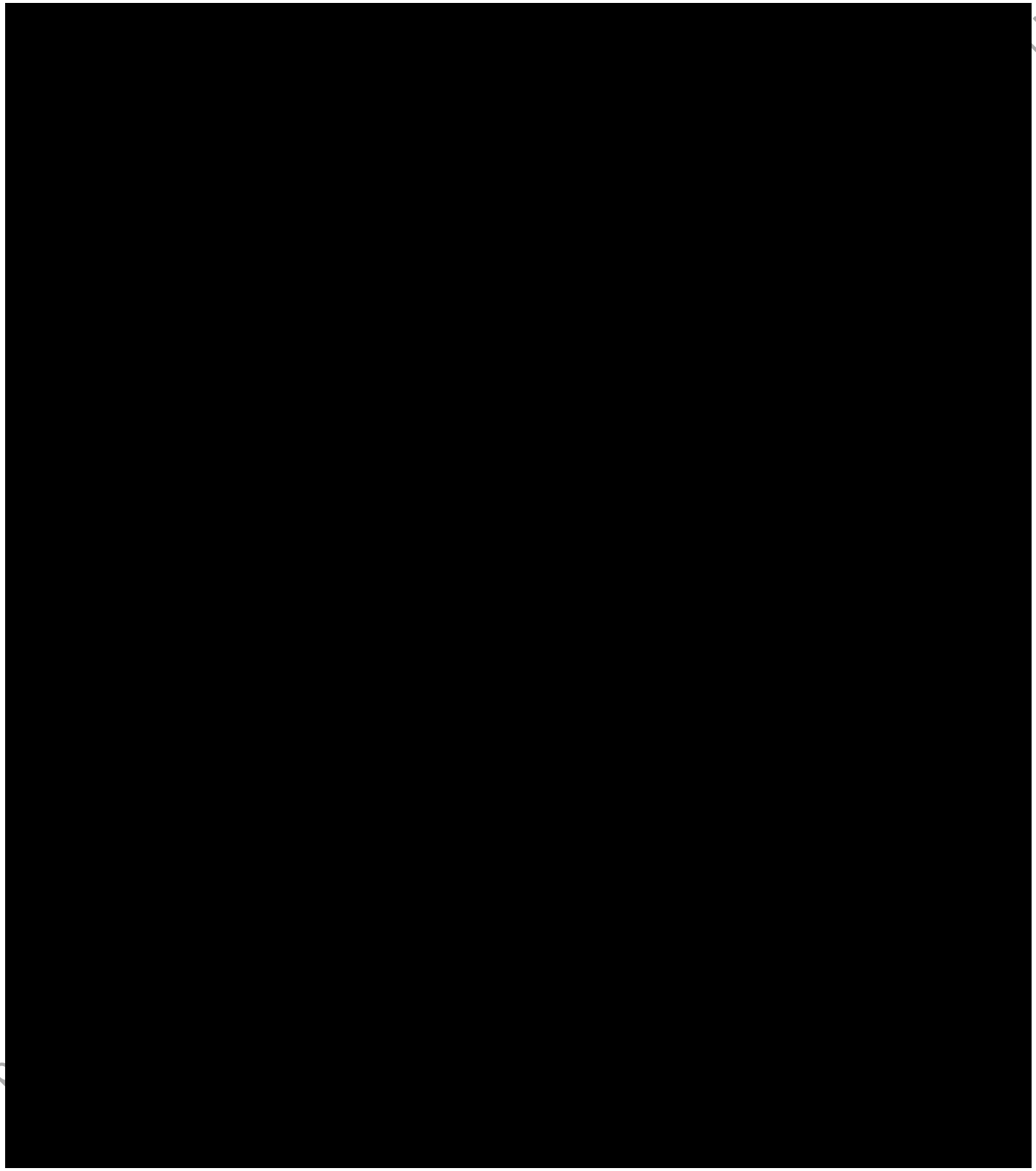
DOR assessed by the investigator

Analytical Methods:

For DOR assessed by the investigator, the analysis method described in section 6.1.3 will be used for Phase 2 part.

[redacted]





### 6.5.4 Sensitive Analyses

As an additional sensitivity analysis, PFS will be re-assessed by using the Investigator's radiological and clinical assessments. In the CRF, if "Did the patient experience Symptomatic Deterioration?" = "Yes", then we will say the patient experiencing PD as determined by clinical assessments. In this sensitivity analysis, PFS will be defined as the time from the date of the first dose until the date of PD by radiological or clinical assessment, or death from any cause, whichever occurs first, as determined by the Investigator. If PD is noted in both clinical and radiological assessments, the first date where PD is noted will be used for analysis.

- Subjects who didn't have baseline tumor assessments or postbaseline radiological assessments, and did not die within 105 days and no clinical progression noted, will be censored on Day 1.
- Subjects who receive new anti-cancer therapy (including palliative radiotherapy during study treatment) prior to PD or death will be censored on the date of last radiological assessment prior to the start of the new anticancer therapy.
- Subjects who experience PD or death after missing 2 or more consecutive radiological assessments will be censored on the date of last RECIST assessment.
- Subjects who experience no documented disease progression or death will be censored on the last radiological assessment.
- When an analysis cutoff date is implemented, only data (deaths and radiological assessments) occurring on or prior to the cutoff date will be used for analysis.

Analysis Set:

Full Analysis Set

Analysis Variables:

PFS by Investigator's Radiological and Clinical Assessments

PFS assessed by the BICR

ORR assessed by the BICR

BOR assessed by the BICR

DOR assessed by the BICR

TTR assessed by the BICR

Analytical Methods:

(1) For PFS re-assessed by using the Investigator's radiological and clinical assessments, the analysis method described in section 6.1.3 will be used for Phase 2 part.

(2) For PFS assessed by the BICR the analysis method described in section 6.1.3 will be used for Phase 2 part.

(3) For ORR assessed by the BICR in Phase 2 part, point estimate and the 2-sided 90% exact CI based on the Clopper-Pearson interval method will be provided by using full analysis set. BOR by investigator assessment will be summarized using the categories of CR, PR, SD, PD, NE. A waterfall plot and swimmer plot will also be provided.

(4) For DOR assessed by the BICR, the analysis method described in section 6.1.3 will be used for Phase 2 part. Time to response, as assessed by the BICR, will be summarized using the descriptive statistics. The analysis of time to response will only include patients with confirmed CR or confirmed PR.

## 6.6 Safety Analysis

### 6.6.1 Adverse Events

- TEAEs are defined as AEs after administration of the first dose of study drug, and through 30 days after the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever occurs first.
- TEAE leading to study drug modification: any TEAE leading to dose reduction, dose delayed or infusion interruption.
- TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

#### *6.6.1.1 Overview of Treatment-Emergent Adverse Events*

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

CTCAE Grade [All Grades, Grade 3+]

Analytical Methods:

The following summaries will be provided for Phase 1 and Phase 2.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number and percentage of subjects)
2) Study Drug Related Treatment-Emergent Adverse Events (number and percentage of subjects)
3) Serious Treatment-Emergent Adverse Events (number and percentage of subjects)
4) Study Drug Related Serious Treatment-Emergent Adverse Events (number and percentage of subjects)
5) Treatment-Emergent Adverse Events Resulting in Study Drug Dose Reduction (number and percentage of subjects)
6) Treatment-Emergent Adverse Events Resulting in Study Drug Dose Delayed (number and percentage of subjects)
7) Treatment-Emergent Adverse Events Resulting in Study Drug Infusion Interruption (number and percentage of subjects)
8) Study Drug Related Treatment-Emergent Adverse Events Resulting in Study Drug Dose Reduction (number and percentage of subjects)
9) Study Drug Related Treatment-Emergent Adverse Events Resulting in Study Drug Dose Delayed (number and percentage of subjects)
10) Study Drug Related Treatment-Emergent Adverse Events Resulting in Study Drug Infusion Interruption (number and percentage of subjects)
11) Treatment-Emergent Adverse Events Resulting in Study Drug Discontinuation (number and percentage of subjects)
12) Study Drug Related Treatment-Emergent Adverse Events Resulting in Study Drug Discontinuation (number and percentage of subjects)
13) Treatment-Emergent Adverse Events Resulting in Death (number and percentage of subjects)
14) Study Drug Related Treatment-Emergent Adverse Events Resulting in Death (number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects

A subject with multiple occurrences of TEAE will be counted only once.

*6.6.1.2 DLTs During The First Cycle Following Study Drug Infusion*

Analysis Set:

Safety Analysis Set

Analysis Variables:

DLTs During The First Cycle

Analysis Method(s):

DLT will be summarized by system organ class and preferred term for Phase 1 part. A subject with multiple occurrences of DLT within a SOC or a PT will be counted only once. Percentages will be based on the number of subjects in the safety analysis set.

*6.6.1.3 Displays of Treatment-Emergent Adverse Events*

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

CTCAE Grade [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Age [18-64 years, ≥65 years]

Weight [<60kg, ≥60kg]

Seroconversion Status [Treatment-emergent ADA, Treatment-enhanced ADAs, Treatment-unaffected ADA, Seronegative]

Analytical Methods:

The following summaries will be provided using frequency distribution for Phase 1 and Phase 2 part.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and CTCAE Grade
(2) Treatment-Emergent Adverse Events System Organ Class and Preferred Term
(3) Treatment-Emergent Adverse Events by Preferred Term
(4) Treatment-Emergent Adverse Events by Preferred Term and CTCAE Grade
(5) Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(7) Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(9) Drug-Related Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(10) Treatment-Emergent Adverse Events Leading to Drug Discontinuation by System Organ Class and Preferred Term

(11) Drug-Related Treatment-Emergent Adverse Events Leading to Drug Discontinuation by System Organ Class and Preferred Term

(12) Treatment-Emergent Adverse Events Leading to Dose Reduction by System Organ Class and Preferred Term

(13) Drug-Related Treatment-Emergent Adverse Events Leading to Dose Reduction by System Organ Class and Preferred Term

(14) Treatment-Emergent Adverse Events Leading to Dose Delayed by System Organ Class and Preferred Term

(15) Drug-Related Treatment-Emergent Adverse Events Leading to Dose Delayed by System Organ Class and Preferred Term

(16) Treatment-Emergent Adverse Events Leading to Infusion Interruption by System Organ Class and Preferred Term

(17) Drug-Related Treatment-Emergent Adverse Events Leading to Infusion Interruption by System Organ Class and Preferred Term

(18) Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term

(19) Drug-Related Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term

(20) Treatment-Emergent Adverse Events by Seroconversion Status, System Organ Class and Preferred Term

(21) Treatment-Emergent Adverse Events by Preferred Term (Age Subgroup Analysis)

(22) Treatment-Emergent Adverse Events by Preferred Term (Baseline Weight Subgroup Analysis)

The frequency distribution will be provided according to the rules below. Percentages will be based on the number of subjects in the safety population.

Number of subjects

A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. For (1), (4) if a subject with multiple occurrences of TEAE within a PT, it will be counted only once with the worst toxicity grade. Percentages will be based on the number of subjects in the safety analysis set.

*6.6.1.4 Death*

Analysis Set:

Safety Analysis Set

Analysis Variables:

Any Death

Death occurred ≤ 30 Days After Last Dose

Primary Cause of Death Occurred ≤ 30 Days After Last Dose

[Adverse Event, Disease Progression, Unknown, Other]

Death Occurred > 30 Days After Last Dose

Primary Cause of Death Occurred >30 Days After Last Dose

[Adverse Event, Disease Progression, Unknown, Other]

Analytical Methods:

(1) Summary of Death

Frequency distributions will be provided for Phase 1 and Phase 2 part.

*6.6.1.5 Displays of Adverse Events of Clinical Interest*

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

CTCAE Grade

[Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Non-CTCAE Grade

[Grade 1, Grade 2, Grade 3, Grade 4]

Seroconversion Status

[Treatment-emergent ADA, Treatment-enhanced ADAs, Treatment-unaffected ADA, Seronegative]

Analytical Methods:

The following summaries will be provided using frequency distribution for Phase 1 and Phase 2 part.

(1) Ocular Treatment Emergent Adverse Events by Preferred Term and CTCAE Grade

(2) Grade 3 or Higher Ocular Treatment Emergent Adverse Events by Preferred Term

(3) Peripheral Neuropathy Treatment Emergent Adverse Events by Preferred Term and CTCAE Grade

(4) Grade 3 or Higher Peripheral Neuropathy Treatment Emergent Adverse Events by Preferred Term

(5) Pneumonitis Treatment Emergent Adverse Events by Preferred Term and CTCAE Grade

(6) Grade 3 or Higher Pneumonitis Treatment Emergent Adverse Events by Preferred Term

(7) Treatment Emergent Adverse Events within 3 Days of Infusion by System Organ Class and Preferred Term (SMQ Hypersensitivity, Narrow + PTs)

(8) Treatment Emergent Adverse Events within 3 Days of Infusion by Seroconversion Status, System Organ Class and Preferred Term (SMQ Hypersensitivity, Narrow + PTs)

(9) Corneal Treatment Emergent Adverse Events by Preferred Term and CTCAE Grade

(10) Corneal Treatment Emergent Adverse Events by Preferred Term and Non-CTCAE Grade

Number of subjects

A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. For (1), (2), (4), (8), (9), if a subject with multiple occurrences of TEAE within a PT, it will be counted only once with the worst toxicity grade category. Percentages will be based on the number of subjects in the safety analysis set.

#### *6.6.1.6 Time to First Onset of Adverse Events of Clinical Interest*

Analysis Set:

Safety Analysis Set

Analysis Variables:

Time to First Onset of TEAE

Patients Experienced TEAEs

Number of Actions Taken with Respect to TEAE

[With One Action Taken, With More Than One Action Taken]

Action Taken

[Drug Permanently Discontinued, Dose Reduced, Infusion Interrupted, Dose Delayed]

Worst Outcome

[Drug Permanently Discontinued, Dose Reduced, Infusion Interrupted, Dose Delayed, No Action Taken]

Analysis Methods:

The following summaries will be provided using frequency distribution and summary statistics for Phase 1 and Phase 2 part.

(1) Ocular TEAE

(2) Corneal TEAE

(3) Peripheral Neuropathy TEAE

(4) Pneumonitis TEAE

For Number of Actions Taken with Respect to TEAE, patient number and percentage will be calculated, the percentage is based on the patients who experienced the corresponding TEAE.

For Action Taken, the number and percentage will be provided, the percentage is based on the safety analysis set.

For Worst Outcome, the number and percentage will be calculated, and the percentage will be based on the safety analysis set.

For (1), Time to First Onset of TEAE, Action Taken and Worst Outcome will also be summarized for each grouped PT.

*6.6.1.7 Resolution of Adverse Events of Clinical Interest*

Analysis Set:

Safety Analysis Set

Analysis Variables:

Resolution of Adverse Events of Clinical Interest

[Complete Resolution, Partial Improvement, No Documented Improvement]

Categories:

CTCAE Grade

[Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Analysis Methods:

The following summaries will be provided using frequency distribution for Phase 1 and Phase 2 part.

(1) Resolution of Ocular Treatment Emergent Adverse Events

(2) Resolution of Corneal Treatment Emergent Adverse Events

(3) Resolution of Peripheral Neuropathy Treatment Emergent Adverse Events

For (1) , its resolution will be summarized by grouped PT, the final resolution status and CTCAE grade, and percentage is also based on total patient number in each grouped PT. For (2) and (3), its resolution will be summarized by the final status and CTCAE grade. If the final status of adverse event is complete resolution, the final grade will be omitted.

### 6.6.2 Other Safety Analysis

#### *6.6.2.1 Best Corrected Visual Acuity*

Analysis Set:

Safety Analysis Set

Analysis Variables:

Baseline BCVA [Not Missing, Missing]

Ocular TEAEs

Ocular TEAEs Categories

[Still on Treatment, Had EOT/30d Exams, Missing EOT/30d Eye Exam, EOS Reason = Death, Ocular AE Final Grade =0, Ocular AE Final Grade =1, Ocular AE Final Grade =2, Ocular AE Final Grade =3]

Worst BCVA Shift

[≥3 Lines of Improvement, ≥2 Lines to <3 Lines of Improvement, ≥1 to <2 Lines of Improvement, Less Than One Line Change in Visual Acuity, ≥1 to <2 Lines of Worsening, ≥2 Lines to <3 Lines of worsening, ≥3 Lines of Worsening]

Had Both Baseline And EOT/30d

BCVA Shift at EOT/30d

[≥3 Lines of Improvement, ≥2 Lines to <3 Lines of Improvement, ≥1 to <2 Lines of Improvement, Less Than One Line Change in Visual Acuity, ≥1 to <2 Lines of Worsening, ≥2 lines to <3 Lines of Worsening, ≥3 Lines of Worsening]

Analytical Methods:

The following analysis will apply to both the Phase 1 and Phase 2 part.

For Baseline of BCVA, the number and percentage for each category will be calculated, the percentage will be based on the safety analysis set.

For Ocular TEAEs, the number and percentage will be calculated, the percentage will be based on the safety analysis set.

For Ocular TEAEs categories, the percentage will be calculated based on the number of patients who experienced Ocular TEAEs.

For Worst BCVA Shift, the number and percentage will be calculated, the percentage will be based on the population who have both baseline and at least one post baseline assessment.

For variable "Had Both Baseline and EOT/30d exams", the number and percentage will be calculated, the percentage will be based on the population who have both baseline and at least one post baseline assessment.

For BCVA Shift at EOT/30d, the number and percentage for each category will be calculated, the percentage will be based on the number of patients with both baseline and EOT/30d assessment.

*6.6.2.2 Intraocular Pressure*

Analysis Set:

Safety Analysis Set

Analysis Variables:

Baseline Intraocular Pressure

Patients with Both Baseline And at Least One Post-baseline

Intraocular Pressure Elevation [≥7 mmHg Elevation Post-baseline, ≤22 mmHg at Baseline and >22 mmHg Post-baseline, ≥7 mmHg Elevation at EOT/30d, ≤22 mmHg at Baseline and >22 mmHg at EOT/30d]

Intraocular Pressure [≤22 mmHg, >22 mmHg, Missing]

Analytical Methods:

All the variables will be analyzed for the right eye and the left eye separately, for both Phase 1 and Phase 2 parts.

(1) Each analysis variable except for intraocular pressure will be summarized separately for the right eye and the left eye, for both Phase 1 and Phase 2 parts. For categories in Intraocular Pressure Elevation, the percentage will be calculated based on the number of patients with both baseline and at least one post-baseline.

(2) For Intraocular Pressure, shift tables showing the number of subjects in each category of intraocular pressure at baseline and the worst post-baseline will be provided for right eye and left eye separately.

6.6.2.3 Hematology and Serum Chemistry

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hematology

[Hemoglobin, Hematocrit, Platelets, Leukocytes (WBC)]

Serum Chemistry

[Albumin, Alkaline phosphatase, ALT, AST, BUN or Urea, Calcium, Chloride, Creatinine, Glucose, Magnesium, Phosphorus, Potassium, Sodium, Total bilirubin]

Categories:

CTCAE Grade [Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]

Analytical Methods:

For each variable, shift tables showing the number of subjects in each category of toxicity grade at baseline and the worst post-baseline will be provided for Phase 1 and Phase 2 part. For WBC Differentials (Neutrophils/Leukocytes, Eosinophils/Leukocytes, Lymphocytes/Leukocytes) the grade will be presented in listing.

*6.6.2.4 Liver Function*

Analysis Set:

Safety Analysis Set

Analysis Variables:

Aspartate Aminotransferase (AST)

[> 3 x ULN, > 5 x ULN, > 10 x ULN, > 20 x ULN]

Alanine Aminotransferase (ALT)

[> 3 x ULN, > 5 x ULN, > 10 x ULN, > 20 x ULN]

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT)

[> 3 x ULN, > 5 x ULN, > 10 x ULN, > 20 x ULN]

Total Bilirubin (TBL)

[> 1.5 x ULN, > 2 x ULN]

Alkaline Phosphatase (ALP) [> 1.5 x ULN]

(AST or ALT) and TBL (concurrent)

[AST or ALT > 3 x ULN and TBL > 1.5 x ULN, AST or ALT > 3 x ULN and TBL > 2 x ULN]

(AST or ALT) and ALP and TBL (concurrent)

[AST or ALT > 3 x ULN and ALP < 2 x ULN and TBL > 2 x ULN]

Analytical Methods:

This summary is based on the maximum lab value among visits including unscheduled visits for each patient. Frequency distributions will be provided for Phase 1 part and Phase 2 part. For each variable, the total number of patients who have non-missing baseline and at least 1 non-missing post-baseline value will be present. And the percentage for each category is based on the total number of patients for a given variable. Concurrent means that all the associated liver function tests must be from the same visit.

### 6.6.3 Extent of Exposure and Compliance

#### *6.6.3.1 Study Drug Exposure*

Analysis Set:

Safety Analysis Set

Analysis Variables:

Number of Doses Received

Number of Cycles Received

Number of Cycles Received Categories [≥1 Cycle, ≥2 Cycles, ≥3 Cycles, ≥4 Cycles, ≥5 Cycles, ≥6 Cycles, ≥7 Cycles, ≥8 Cycles, ≥9 Cycles, ≥10 Cycles]

Total Cumulative Dose (mg)

Duration of Dosing (weeks)

Duration of Dosing (months)

Absolute Dose Intensity (mg/kg/dose)

Relative Dose Intensity (% of planned)

Analytical Methods:

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided for Phase 1 part and Phase 2 part. For "Number of Cycles Received" categories, the percentage will be based on the safety analysis set.

*6.6.3.2 Dose Modifications*

Analysis Set:

Safety Analysis Set

Analysis Variables:

Patients with Any Dose Modification

[Any Dose Reduction, Any Infusion Interruption, Any Dose Delayed]

Patients with Any Dose Reduction

Patients with Any Dose Reduction Categories [1, 2, ≥3]

Reason for Dose Reduction [Adverse Event, Other]

Patients with Any Infusion Interruption

Patients with Any Infusion Interruption Categories [1, 2, ≥3]

Reason for Infusion Interruption [Adverse Event, Other]

Patients with Any Dose Delay

Patients with Any Dose Delay Categories [1, 2, ≥3]

Reason for Dose Delay [Adverse Event, Other]

Analytical Methods:

Frequency distributions will be provided for Phase 1 part and Phase 2 part.

## 6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

The analyses of PK endpoints will be described in the Clinical Pharmacology Analysis Plan.

## 6.8 Other Analyses

### 6.8.1 Immunogenicity Analysis

Analysis Set:

Patients Who Have Both Pre-dose and Post-dose Immunogenicity Data

Analysis Variables:

Seronegative

Treatment-emergent ADA

Treatment-unaffected ADA

Treatment-enhanced ADAs

Patients with Negative NAb at Baseline and Negative NAb at Post Treatment

Patients with Negative NAb at Baseline and Positive NAb at Post Treatment

Patients with Positive NAb at Baseline and Negative NAb at Post Treatment

Patients with Positive NAb at Baseline and Positive NAb at Post Treatment

Analytical Methods:

Frequency distributions will be provided for Phase 1 part and Phase 2 part.

### 6.8.2 New Anticancer Therapy

Analysis Set:

Safety Analysis Set

Analysis Variables:

Patients Receiving New Anticancer Therapy

Analytical Methods:

Frequency distributions will be provided for Phase 1 part and Phase 2 part.

## 6.9 Interim Analyses

Not appliable.

## 6.10 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not appliable.

# 7.0 REFERENCES

Not appliable.

# 8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not appliable.

# 9.0 CHANGES FROM THE PREVIOUS VERSION OF THE SAP

- In section 6.2.3, we have updated the categories for the study status of "Disposition of Subjects" in Phase 1, where the follow-up period after PD is optional.

- In section 6.2.4.2, we have deleted the reason categories for subjects excluded from each analysis set.
- In section 6.3.2, "Baseline Characteristics", we have updated the categories of "Number of Prior Lines of Therapy" for Phase 1 and variables related to BRCA. We have also removed the variables "Number of Prior Regimens" and "Treatment Setting".
- In section 6.4.1, we have changed the variable from "Prior Medication" to "Prior Anticancer Therapy."
- In sections 6.5.1, 6.5.2, and 6.5.3, we clarified that the efficacy endpoints are assessed by the investigator.
- In sections 6.5.1.3, we have modified the category of BRCA Status into (BRCA1 and/or BRCA2 Positive, Negative/Unknown) for subgroup analysis.
- In section 6.5.3.6, we have added an analysis of the concordance of BOR between the investigator and BICR as a sensitivity analysis.
- In section 6.5.4, we have included efficacy endpoints assessed by BICR as sensitive analysis.
- In section 6.6.1.5, we have added an analysis for Grade 3 or higher ocular TEAEs.
- In section 6.6.1.6, section 6.6.1.7, we have deleted corneal AE's analysis for grouped PT.
- In section 6.6.2.3, we have deleted the variable erythrocytes (RBC) in Hematology and updated the analysis for WBC differentials.
- In section 6.8.1 on immunogenicity, we have updated the variable label for ADA and incorporated an analysis of neutralizing antibodies (NAb).