A Single-Arm, Multicenter, Phase Ib/II Clinical Study of Toripalimab (JS001) Combined with Cetuximab in the Treatment of Advanced Squamous Cell Carcinoma of Head and Neck

Protocol No.: JS001-037-Ib/II-HNSCC

Statistical Analysis Plan

Version No.: 1.0

Date: November 25, 2024

The blackened parts below are the names of the project team members, aiming to protect personal information.

Version changes in the statistical analysis plan

Rev. #	Version Date	Revision history	Modified by
V1.0	November 25,2024	Not applicable	[redacted]

Sign Page for Statistical Analysis Plan

Study Title:	A Single-Arm, Multicenter, Phase Ib/II Clinical Study of Toripalimab (JS001) Combined with Cetuximab in the Treatment of Advanced Squamous Cell Carcinoma of Head and Neck
Protocol No.:	JS001-037-Ib/II-HNSCC
Version/Date of Statistical Analysis Plan:	1.0 / 2024/11/25

[redacted]

Shanghai Junshi Biosciences Co., Ltd. Signature Date
Principal Statistician

[redacted]

Shanghai Junshi Biosciences Co., Ltd. Signature Date
Statistical Programming

[redacted]

Shanghai Junshi Biosciences Co., Ltd. Signature Date
Director of Statistics

[redacted]

Shanghai Junshi Biosciences Co., Ltd. Signature Date
Senior Medical Manager

[redacted]

Shanghai Junshi Biosciences Co., Ltd. Signature Date
Senior Clinical Pharmacology Manager

Contents

List of Abbreviations

Abbreviations	**DEFINITIONS**
ADA	Anti-drug Antibody
ADAS	Immunogenicity Analysis Set
AE	Adverse Event
AFP	AFP
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BOR	Best Response
CI	Confidence interval
CK-MB	Serum creatine kinase isoenzyme
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRF	Case Report Form
DCR	Disease control rate
DoR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
HBcAb	HBV core antibody
HBeAb	Hepatitis B virus e antibody
HBeAg	HBV e Antigen
HBsAb	HBV surface antibody
HBsAg	HBV surface antigen
HCC	Hepatocellular carcinoma
HR	Hazard ratio
ICH	International Conference on Harmonisation
irAE	Immune-related Adverse Event
IRC	Independent Review Committee
iRECIST	Immune Response Evaluation Criteria in Solid Tumour
LVEF	Left ventricular ejection fraction
MAX	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MIN	Minimum
Nab	Neutralising antibodies
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse

Abbreviations	**DEFINITIONS**
	Events
ORR	Objective Response Rate
OS	Overall Survival
PD	Disease progression
PD-L1	Programmed Cell Death-Ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
PKCS	Pharmacokinetic Concentration Set
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SD	Standard deviation
SIE	Adverse Events of Special Interest
SOC	System Organ Class
SS	Safety Analysis Set
TEAE	Treatment-emergent Adverse Event
TTP	Time to Disease Progression

1 Introduction

This Statistical Analysis Plan (SAP) is specifically developed for the clinical study project of Toripalimab (JS001) in combination with cetuximab for the treatment of advanced head and neck squamous cell carcinoma, a single-arm, multi-center, phase Ib/II clinical study. This SAP includes the analysis population definition, derived variables, and statistical analysis methods. This SAP is written based on the protocol version 4.0 (September 13, 2024).

1.1 Study Objectives

Primary objective of Phase Ib study:

- To evaluate the safety and tolerability of toripalimab combined with cetuximab (hereinafter referred to as the "combination regimen") in patients with recurrent or metastatic HNSCC.

Secondary objectives of Phase Ib study:

- To determine the recommended phase II dose (RP2D) of the combined regimen for treatment of recurrent or metastatic HNSCC;
- To evaluate the pharmacokinetic (PK) profile of the combination regimen in patients with recurrent or metastatic HNSCC;
- To evaluate the efficacy of the combination regimen in the treatment of recurrent or metastatic HNSCC;

Primary objective of Phase II study:

- The efficacy of the combination regimen in patients with recurrent or metastatic HNSCC will be evaluated by objective response rate (ORR) according to Response Evaluation Criteria in Solid tumor version 1.1 (RECIST 1.1).

Secondary objectives of Phase II study:

- To evaluate the efficacy of the combined regimen in terms of disease control rate (DCR), duration of response (DOR) and progression-free survival (PFS) in patients with recurrent or metastatic HNSCC;
- To evaluate the efficacy of the combination regimen in patients with recurrent or metastatic HNSCC by measuring overall survival (OS) and 1-year OS rate.
- To further evaluate the safety and tolerability of the combination regimen in the treatment of recurrent or metastatic HNSCC.

Exploratory study objectives (applicable to Ib and phase II study stage):

- To evaluate the efficacy of the combination regimen in patients with recurrent or metastatic HNSCC using Immune-related Response Evaluation Criteria in Solid tumor (iRECIST).
- Test biomarkers and evaluate their relationship with efficacy
- To evaluate the immunogenicity of JS001 and cetuximab.

1.2 Study Design

This is an open-label, multi-center Phase Ib/II clinical study. The Phase Ib study phase is used to evaluate the safety of toripalimab combined with cetuximab in the treatment of recurrent or metastatic HNSCC after failure of first-line platinum-based chemotherapy and to determine the recommended Phase II dose (RP2D); the Phase II study phase is divided into two cohorts, i.e., cohort A is used to evaluate the efficacy and safety of the combination regimen in the treatment of recurrent or metastatic HNSCC after failure of first-line platinum-based chemotherapy; cohort B is used to evaluate the efficacy and safety of the combination regimen in the treatment of PD-L1-positive HNSCC without previous systemic therapy for recurrent or metastatic disease.

Phase Ib:

A cycle consists of 21 days. Toripalimab will be administered on Day 1, and cetuximab will be administered after an observation period of approximately 60 minutes. The specific dose is listed in the table below:

Dose group	**Investigational product**	**Every cycle (21 days)**		
		Day 1	**Day 8**	**Day 15**
Initial dose group	Toripalimab	240 mg	/	/
	Cetuximab	500 mg/m^2 after 400 mg/m^2 in the 1st cycle	250 mg/m^2	250 mg/m^2

Alternate dose group	Toripalimab	240 mg	/	/
	Cetuximab	After 400 mg/m^2 in the first cycle, 200 mg/m^2 in subsequent cycles	200 mg/m^2	200 mg/m^2

First, 6 patients were enrolled to receive the initial dose as the tolerability observation period of the first cycle (21 days). If DLT occurred in <2 patients, then 6 patients were enrolled (total 12 patients) to collect sufficient safety and PK data of the combination therapy. The safety monitoring committee (SMC) would determine whether the recommended dose for phase II is based on the safety and PK data of the 12 patients.

If ≥2 patients experience DLT in the first 6 patients, the dose will be adjusted to the alternative dose and then the patients will be enrolled and observed according to the enrollment plan above. If ≥2 patients experience DLT in the first 6 patients in the alternative dose group, the Safety Monitoring Committee (SMC) will decide whether to use other dose levels/dose cycles for the study based on the safety and PK data obtained.

Phase II:

Patients who participate in the Phase II study period will receive toripalimab in combination with cetuximab at the RP2D established in the Phase 1b study. Treatment will continue until radiographic disease progression according to RECIST v1.1 as determined by the investigator, intolerable toxicity, patient withdrawal of consent, investigator's decision for treatment withdrawal, or up to 2 years of treatment, whichever occurs first.

The Phase II Cohort A will adopt Simon's two-stage design. In the first stage of Cohort A, 24 subjects will be enrolled (including those from the Phase I study at the same dose). If ⩾6 subjects achieve response (defined as a complete response or partial response

assessed per RECIST 1.1), the second stage of Cohort A will be initiated, enrolling an additional 21 subjects. A total of 45 subjects will be enrolled in Cohort A.

The Phase II Cohort B will also utilize Simon's two-stage design. In the first stage of Cohort B, 23 subjects will be enrolled. If ≥7 subjects achieve response (defined as a complete response or partial response assessed per RECIST 1.1), the second stage of Cohort B will commence, enrolling an additional 20 subjects. A total of 43 subjects will be enrolled in Cohort B.

1.3 Sample Size

The sample size for the Phase Ib study depends on the number of dose arms and the number of DLTs. At least 12 patients are required to determine the recommended Phase II dose.

In Phase II study, Simon two-stage design was used, and the sample size was based on the primary endpoint of the study. The objective response rate (ORR) evaluated by the IRC according to RECIST v1.1 criteria was calculated as follows:

The null hypothesis for cohort A is that the ORR is equal to 20%. Assuming the ORR of toripalimab in combination with cetuximab is 40%, the sample size is estimated using the minimax method. 24 patients are required to be enrolled in the first stage. If the number of patients with response is less than or equal to 5, the cohort will be terminated. Otherwise, 21 additional patients are required to be enrolled until a total of 45 patients are enrolled. At a significance level of 0.05 (2-sided) and power of 90%, the null hypothesis will be rejected if the number of patients with response is greater than 13 out of all patients.

The null hypothesis for cohort B is that the ORR is equal to 25%. It is assumed that the ORR of toripalimab in combination with cetuximab is 43%. The sample size is estimated using the minimax method. 23 subjects will be enrolled in the first stage. If the number of subjects with an effective response is less than or equal to 6, this cohort will be terminated. Otherwise, 20 additional subjects will be enrolled until a total of 43 subjects are enrolled. At a significance level of 0.05 (2-sided) and a power of 80%, the null hypothesis will be rejected if the number of subjects with an effective response is greater than 15 out of all subjects.

2 Statistical Hypothesis and Multiplicity

Not applicable.

3 Endpoints

3.1 Primary Endpoints

Phase Ib study

- Incidence and severity of Adverse Events (AEs) and serious Adverse Events (SAEs) as assessed by NCI-CTCAE 5.0, and vital signs, Electrocardiogram, and Laboratory test abnormal.

Phase II study:

- Cohort A: ORR assessed by IRC according to RECIST v1.1.
- B Cohort B: ORR assessed by investigators according to RECIST 1.1

3.2 Secondary Endpoints

Phase Ib study:

- Recommended Phase II dose (RP2D) for the combination regimen.
- PK parameters of toripalimab and cetuximab, including clearance (CL), volume of distribution (Vss), AUC, Cmax, Ctrough and t1/2.
- ORR, DCR, DOR and PFS assessed by IRC and investigators according to RECIST 1.1.
- OS and 1-year OS rate.

Phase II study:

- Cohort A: ORR assessed by investigators according to RECIST 1.1.
- Cohort A: DCR, DOR and PFS assessed by IRC and by the investigator according

to RECIST 1.1.

- Cohort B: DCR, DOR and PFS assessed by the investigator according to RECIST 1.1

- OS and 1-year OS rate.

- Incidence and severity of Adverse Events (AEs) and serious Adverse Events (SAEs) as assessed by NCI-CTCAE 5.0, and vital signs, Electrocardiogram, and Laboratory test abnormal.

3.3 Exploratory Endpoint

- iORR, iDCR, iDOR, and iPFS evaluated according to iRECIST.

- Correlation between PD-L1 expression, HPV status (only applicable to oropharyngeal cancer), tumor mutation burden and efficacy.

- The positivity of anti-tocilizumab and anti-rituximab antibodies will be analyzed in combination with PK parameters and safety and efficacy data.

4 Analysis Sets

Full analysis set (FAS) includes all patients who have received at least one dose of toripalimab injection.

The Safety analysis Set (SS) includes all patients who have received at least one dose of toripalimab. SS is the primary analysis set for safety, immunogenicity, pharmacodynamics and biomarker analyses.

The Efficacy Evaluable Analysis Set (EAS) includes patients who have received at least one dose of toripalimab injection, and have baseline and at least 1 post-baseline tumor evaluation data.

The PK Concentration analysis Set (PKCS) included all subjects who had received at least one dose of toripalimab or cetuximab and had at least 1 valid concentration data.

The PK parameter Set (PKPS) includes all subjects who have received at least one dose

toripalimab or cetuximab and have at least 1 valid PK parameter.

The Anti-Drug Antibody analysis set (ADA) included all patients who received at least one dose of toripalimab or cetuximab and had baseline and at least one post-baseline ADA evaluation data.

The Dose-Limiting Toxicity analysis set (DLT) includes all patients who have received at least one dose of the study drug, completed the first cycle of treatment, or withdrew from the study prematurely due to Adverse Events during the first cycle of treatment.

5 Statistical Analysis

5.1 General principles

The study mainly used descriptive statistical analysis, and did not involve statistical hypothesis and test.

All statistical analyses and reporting will be completed using SAS 9.4 (or a higher version).

In the descriptive analysis items, quantitative data were described by number of patients, mean, median, maximum, and minimum. If the summarized number was less than or equal to 3, only number of patients, mean, maximum, and minimum were provided. Categorical data were described by frequency and percentage. Time-to-event variables were summarized according to data characteristics by Kaplan-Meier nonparametric maximum likelihood method or descriptive method. The number of patients with each type of event and the number of censored patients were also presented. The number of decimal places for descriptive statistics was not more than 4, and the selection principle was shown in the following table:

Name	**Explanation**	**Decimal places**
N	Number of subjects in the analysis set	Always show as 0
n	Number of subjects with complete results	Always show as 0
%	Percent	Categorization shows as 1 person
Mean	Arithmetic mean	One more decimal place than the raw data
SD	Standard deviation calculated with unbiased variance	Two more decimal places than the raw data

CV%	Variable Coefficient	Two more decimal places than the raw data
Median	Median	One more decimal place than the raw data
Min.	Minimum	Same as the raw data
Max.	Maximum	Same as the raw data
GeoMean	Geometric mean	One more decimal place than the raw data
GeoCV%	Geometric Variable Coefficient	Two more decimal places than the raw data
Q1	First quartile	One more decimal place than the raw data
Q3	First, second, and third quartiles	One more decimal place than the raw data

If necessary, the conversion of days to months will use the formula: Months = Days / 30.4375; the conversion of days to years will use the formula: Years = Days / 365.25; the conversion of days to weeks will use the formula: Weeks = Days / 7.

5.2 Analysis Group

Unless otherwise specified, baseline data, concomitant medications and non-drug therapies, drug exposure and Adverse Event analyses will be performed by the dose group in which the subject participated in the trial. The specific analysis groups are as follows.

1) Phase Ib: initial dose (toripalimab 240 mg+ cetuximab 400+ 250 mg/m^2), alternative dose (toripalimab 240 mg+ cetuximab 400+ 200 mg/m^2)

2) Phase II: <Actual selected> Dose Cohort A, <Actual selected> Dose Cohort B.

For listings, unless otherwise specified, all subject data should be listed rather than based on a specific analysis set.

5.3 Definition of baseline

Baseline is defined as the status of patients prior to the first dose. For tests that are not recorded in hours and minutes, the test results on the day of the first dose can be used as the baseline. Changes from baseline will be calculated as: the value at the relevant time point - baseline value. For safety assessments, the baseline in this study is defined as the last collection of safety data prior to the subject receiving the investigational product. For tumor assessment, the last assessable radiological examination within 4 weeks before the first dose is used as the tumor assessment result at baseline.

5.4 Study days

The date of the first dose of the investigational drug is recorded as Day 1. If the test value or event occurs before the first dose, the study day relative to the first dose = date of the test value or event - date of the first dose; if the test value or event occurs after the first dose, the study day relative to the first dose = date of the test value or event - date of the first dose + 1.

5.5 Baseline data analysis

All baseline data analyses were based on the full analysis set unless otherwise specified.

5.5.1 Subject disposition

Subject disposition was summarized based on all subjects.

The number of screened, unscreened, enrolled, treated, and completed first 21-day safety patients will be summarized. The reasons and proportions for screening failure will be summarized.

Screening failures and successful subjects will be listed separately, and the enrollment of each subject in each analysis set will be marked in the list of successful subjects.

Number of subjects are summarized in each analysis set.

5.5.2 Demographic characteristics and other baseline data

Summarize and list the following demographic information:

Descriptive statistics will be summarized by measurement variables: age, height, weight, BMI, BSA;

The descriptive statistics of categorical variables were summarized as follows: gender, ethnicity, age (18~65, >=65), smoking status, and drinking status.

All baseline characteristics collected on the CRF will be tabulated. The following baseline characteristics will be summarized:

Descriptive statistics of categorical variables: serum virology test results (hepatitis B

five items, HCV antibody, HIV antibody) (negative, positive), allergy history (yes, no), ECOG score (0, 1). PD-L1 test results and previous HPV test results were summarized.

The variables to be summarized by descriptive statistics of measurement variables include: left ventricular ejection fraction (LVEF), HBV DNA, HCV RNA.

5.5.3 medical history

Neoplasm and non-neoplasm histories will be summarized separately.
The history of neoplasm and diagnosis are described and summarized as follows:

- Described by categorical variables:
  - Diagnosis information:

    Primary site, tissue type, histological grade at diagnosis.

    Tumor stage at enrollment, TNM stage at enrollment, distant metastasis sites, presence of locally advanced or distant metastasis not amenable to radical treatment, history of recurrence after prior radical therapy, prior antitumor treatment, disease status (including: locally recurrence: recurrence after radical therapy with distant metastasis as M0; recurrence and metastasis: recurrence after radical therapy with distant metastasis as M1; locally advanced: no recurrence after radical therapy with distant metastasis as M0. Analysis was performed only for cohort B).

- Described by quantitative variables:
  - ✓ The disease duration was calculated based on the first diagnosis, i.e., disease duration = (date of informed consent – date of first diagnosis + 1)/365.25.
  - ✓ The duration between the last recurrence and informed consent date, duration between last recurrence and informed consent date = (date of informed consent - date of the last recurrence + 1) / 365.25.
  - ✓ Years since local progression or distant metastasis, Years of metastasis = (date of informed consent – date of local progression + 1) / 365.25.

List all neoplasm history and diagnostic information collected on the CRF.

Medical history of non- neoplasm diseases will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in CRF. The coded data will be summarized by System Organ Class (SOC) and Preferred Term (PT).

5.6 Prior and Concomitant Medications or Non-Drug Therapy

5.6.1 Prior and concomitant medication or non-drug therapy (non-anti-tumor)

The study will collect data on prior drug or non-drug therapies, and concomitant drug or non-drug therapies. The prior and concomitant drug therapy recorded in the CRF will be coded using the latest version of the WHO Drug Dictionary. Prior drug therapy is defined as therapy that ends before the first dose. Concomitant drug therapy is defined as therapy that starts after the first dose or starts before the first dose and ends after the first dose.

For previous and combined medications, ATC2 classification and preferred terms under it will be used. The ATC2 classification will be sorted in alphabetical order, and the preferred terms will be sorted in descending order by the number of patients receiving medication under each ATC2 classification.

All collected information on prior and concomitant medications and non-drug therapies will be listed.

5.6.2 Prior and subsequent medication or non-drug therapy (anti-tumor)

All prior and subsequent antitumor therapy, prior and subsequent antitumor radiotherapy, surgeries (including therapeutic phase, purpose of operation, etc.) will be summarized.

The prior anti-tumor treatment (including drug and non-drug therapies) that occurred before informed consent would be summarized by treatment classification, the number of prior anti-tumor treatments (including recurrence within 6 months after platinum-containing adjuvant therapy, treatment failure of first-line systemic therapy, and treatment failure of second-line systemic therapy) in Phase Ib and Cohort A would be summarized, and the drug therapy and non-drug treatment history of subjects would be summarized and listed.

5.7 Protocol Deviations

The number and proportion of important protocol deviations of each type that occurred during the study will be summarized, and all protocol deviations during the study will be listed.

5.8 Safety analysis

All safety analyses will be based on the safety analysis set unless otherwise specified.

5.8.1 Study Drug Exposures

The analysis of study treatment was performed using the Safety Analysis Set, which summarized the exposure dose of various treatments for all subjects from the first dose to the last dose, and provided a list of drug exposure. The summary items included: actual number of doses, duration of medication, actual cumulative dose, planned cumulative dose, actual dose intensity, and relative dose intensity.

- Actual dose intensity of JS001 (mg/week) = Actual dose /Number of weeks.
- Planned dose intensity (mg/week) = planned dose per cycle/weeks in a cycle.
- Actual dose intensity of cetuximab (mg/m^2/week) = actual dose /BSA (m^2)/weeks, where BSA (m^2) = sqrt([height (cm) × weight (kg)]/3600).
- Intensity of planned doses of cetuximab (mg/m^2/week) = Unit planned dose/Weeks in the cycle.
- Relative dose intensity (%) = actual dose intensity / planned dose intensity × 100%.

5.8.2 Adverse Event

Adverse Events (AEs) are adverse clinical events or exacerbation of pre-existing diseases that occur in patients or clinical trial subjects after receiving the test drug, and do not necessarily have a causal relationship with drug therapy.

Treatment-emergent adverse events (TEAEs) will be summarized. TEAEs are defined as Adverse Events that occur or worsen after the first dose and occur within 60 days after the last dose. When summarizing the incidence of Adverse Events, if the same patient experiences the same Adverse Event multiple times, it is counted as one case unless otherwise specified, and the severity is summarized according to the worst one.

The following TEAEs were summarized:

- Number of patients with TEAEs,
- Treatment-emergent Adverse Event (TEAE)
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- CTCAE grade 3 or higher Adverse Events occurred during treatment
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- Treatment-emergent serious Adverse Events
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- CTCAE grade 3 or higher serious Adverse Events occurred during treatment
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- Treatment-emergent Adverse Event leading to interruption of JS001 or cetuximab
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- Treatment-emergent Adverse Events leading to interruption of JS001 and cetuximab
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- Treatment-emergent Adverse Events leading to suspension of JS001
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab

- Treatment-emergent Adverse Event leading to suspension of cetuximab
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- Treatment-emergent Adverse Event leading to permanent discontinuation of JS001 or cetuximab
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- Treatment-emergent Adverse Events leading to permanent discontinuation of JS001 and cetuximab
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- Treatment-emergent Adverse Events leading to permanent discontinuation of JS001
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- Treatment-emergent Adverse Event leading to permanent discontinuation of cetuximab
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- Treatment-emergent Adverse Events with an outcome of death
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- Immune-related Adverse Event
  - CTCAE grade 3 or higher
- Infusion reaction
  - Related to JS001
  - Related to cetuximab

- CTCAE grade 3 Infusion reaction or above
  - Related to JS001
  - Related to cetuximab
- Adverse Events of special interest
  - Related to the treatment regimen (JS001 and/or cetuximab)
  - Related to JS001
  - Related to cetuximab
- DLT
  - Related to JS001
  - Related to cetuximab
- Maximum intensity treatment-emergent Adverse Events of any grade
  - Grade 1
  - Grade 2
  - Grade 3
  - Grade 4
  - Grade 5

The incidence of Adverse Events was summarized by system organ class (SOC), preferred term (PT), and CTCAE grade. If the same patient experienced the same Adverse event multiple times, the drug-related Adverse Event of the most severe grade was selected for analysis.

List all adverse events.

5.8.3 Adverse Events related to study drug

The investigator should make a comprehensive judgment on the causal relationship (related/unrelated) between the Adverse Event and the study drug based on the understanding of the patient, the clinical background of the event, and any alternative causes, etc. Related means there is a reasonable correlation between the adverse event and the study drug, and unrelated means there is no reasonable correlation between the adverse event and the study drug, but there is an alternative explanation, such as disease progression, concomitant therapy, and other risk factors. The total number of adverse events related to the study drug is used as the numerator, and all the enrolled patients available for adverse reaction evaluation as the denominator to calculate the incidence

of Adverse reactions.

Summarized separately by related to treatment regimen (JS001 and/or cetuximab) as applicable, related to JS001, and related to cetuximab for Adverse Event.

- Number and percentage of patients with Adverse Events that occur after treatment,
- Number and percentage of patients with Adverse Event with CTCAE grade of 3 or above,
- Number and percentage of patients who experienced Adverse Events leading to interruption of JS001 or cetuximab,
- Number and percentage of patients who experienced an Adverse Event leading to permanent discontinuation of JS001 or cetuximab,
- Number and percentage of subjects with Adverse Events with an endpoint of death,

The incidence of adverse events related to the study drug was summarized by system organ class (SOC), preferred term (PT), and CTCAE grade. If the same patient experienced the same adverse reaction multiple times, the most severe drug-related adverse event was selected for analysis, and its outcome was summarized.

5.8.4 Serious Adverse Event

The number and percentage of subjects with SAEs and the number and percentage of subjects with SAEs of Grade 3 or higher according to CTCAE were summarized, and the number and percentage of subjects with serious Adverse Events were calculated by SOC, PT and CTCAE grade. At the same time, serious Adverse Events related to study drug (JS001 and/or cetuximab), JS001 and cetuximab were summarized separately.

List all serious adverse events.

5.8.5 DLT

The incidence of DLT will be analyzed in the DLT analysis set.

Number and percentage of patients with at least one DLT event were summarized.

DLT related to the study drug, JS001 and cetuximab were summarized separately.

Provide a list of all DLT events in the order of subject enrollment, including the relationship to treatment and actions taken.

5.8.6 Adverse Events of special interest

Adverse Events of special interest in this study include:

- Immune-related Myocarditis
- Hepatic function abnormal reaching Hy's law, elevated ALT or AST (> 3 × ULN) combined with elevated Bilirubin total (> 2 × ULN) or clinical jaundice, excluding cholestatic jaundice or other causes of elevated Bilirubin.

The number and percentage of subjects with Adverse Events of special interest will be summarized, and the number and percentage of subjects with serious Adverse Events will be calculated by SOC, PT, and CTCAE grade. At the same time, the Adverse Events of special interest related to the study drug (JS001 and/or cetuximab), JS001, and cetuximab will be summarized separately. All the listings of all adverse events of special interest will be provided in accordance with the subject's enrollment order.

5.8.7 Laboratory test

5.8.7.1 General Laboratory tests

General laboratory test results will be graded if they can be graded according to NCI CTCAE 5.0 criteria. Baseline values, minimum values decreased from baseline, maximum values increased from baseline, and each planned visit point will be summarized. Cross tabulation will be used to summarize the worst results from baseline to the end of the first dose to the end of safety follow-up, and the post-baseline worst CTCAE grade for subjects who become worse from baseline will be summarized. For subjects with clinical assessment results, a cross tabulation of the relative baseline will be drawn based on the clinical assessment.

- Routine blood test: Red blood cell count (RBC), haemoglobin (HB), platelet count (PLT), white blood cell count (WBC), neutrophil count (ANC) and lymphocyte count, etc.;

- Blood biochemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (γ-GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP), blood urea nitrogen (BUN) or urea (preferably blood urea nitrogen), total protein (TP), albumin (ALB), creatinine (Cr), glucose (GLU), K+, Na+, Ca2+, Mg2+, Cl-; creatinine clearance, etc.;
- Routine urinalysis: white blood cells, erythrocytes, protein urine, etc.;
- Coagulation function: including thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR) , etc.;
- Thyroid function: including serum Tri-iodothyronine free (FT3), free T4 (FT4) and thyroid stimulating hormone (TSH) , etc.

The Laboratory tests in the screening period will not be described relative to baseline.

In the above analysis, the summary of examination values and relative changes at each visit point is only included for the data at the planned visit point.

All laboratory test results were listed; all abnormal laboratory test results and their recovery were listed. The worst-case cross-tabulation of changes from baseline needs to be analyzed.

5.8.7.2 Electrocardiogram

Summarize the baseline values, lowest values decreased from baseline, highest values increased from baseline, and values at the last visit for HR, QT interval, QRS interval, PR interval, and QTcB/ QTcF interval.

A cross-tabulation list of the results of the clinical evaluation as compared to baseline will be prepared.

List all ECG results, abnormal Electrocardiogram results and their recovery.

5.8.7.3 Vital Signs

Summarize the baseline values for each vital sign (Blood pressure systolic, Blood pressure diastolic, heart rate, respiratory rate, and body temperature), the lowest decrease from baseline, the highest increase from baseline, and each scheduled visit. Provide a list of all vital signs and their abnormalities.

A cross-tabulation list of the change from baseline was made according to the clinical evaluation results.

5.8.7.4 ECOG

Summarize ECOG scores at each evaluation timepoint; list all ECOG scores.

5.8.8 Other Tests

Provide a list of all tests performed during pregnancy by visit.

5.9 Efficacy Analysis

The efficacy analysis was performed by pooling the data from the Phase Ib, cohort A and cohort B of Phase II separately. All the results of the evaluation of solid tumors were analyzed in accordance with RECIST 1.1. The results evaluated in accordance with iRECIST were presented in a list only. The efficacy analysis will based on the full analysis set and efficacy evaluable analysis set.

Objective Response Rate (ORR): Percentage of subjects who have received the study treatment and have the best response (BOR) of complete response (CR) or partial response (PR) as assessed by RECIST 1.1 and iRECIST, respectively. ORR analysis is only based on the tumor imaging evaluation results that occur prior to receiving prohibited anti-tumor therapy.

Duration of Response (DoR): defined as the date of the first recorded tumor response (assessed as CR or PR according to RECIST 1.1 criteria or iRECIST criteria) to the date of the first recorded objective tumor progression or death due to any cause (whichever comes first). Analysis was limited to tumor imaging assessments that occurred prior to the administration of prohibited antitumor therapy.

BOR is the best response and is defined as the best response recorded between the date of enrollment and the date of objective progression as recorded according to RECIST 1.1 and iRECIST, or the date of start of subsequent antitumor therapy, whichever occurs first. For subjects without recorded progression or subsequent antitumor therapy, BOR will be determined based on all the response assessment results.

Disease Control Rate (DCR): The proportion of subjects who have received study treatment and have been evaluated as Complete Response (CR), Partial Response (PR) and Stable Disease (SD) for Best Overall Response (BOR) according to RECIST 1.1 and iRECIST criteria, respectively. Analysis is only based on tumor imaging evaluation results prior to receiving prohibited anti-tumor therapy.

Progression-free survival (PFS): defined as the time from enrollment to the date of the first documented progression (regardless of continued treatment) or death due to any cause, as determined by RECIST 1.1 and iRECIST criteria.

Overall survival (OS): refers to the time from enrollment to death from any cause.

5.9.1 Tumor Response

The number and percentage of patients with ORR and DCR, as well as the two-sided 95% confidence interval constructed by the Clopper-Pearson exact method were calculated. The results of tumor assessments is required to be confirmed when calculating ORR, BOR, DOR, or DCR, with a confirmation period of at least 4 weeks for complete response or partial response.

In addition, the waterfall chart is drawn according to the optimal change rate of the tumor burden of target lesions, the spider chart is drawn according to the change of the tumor burden of target lesions relative to baseline, and the water flow chart is drawn according to the tumor evaluation results. The target lesion tumor burden is defined as the sum of the diameters of target lesions.

List the assessment data of target, non-target and new lesions; list the overall assessment of lesions.

Table 2 Confirmation Criteria for Response in Solid Tumours

Overall response at time point under confirmation（T1）	Overall response at subsequent time point (T2)	Total response at the time of confirmation
CR	CR + (T2-T1 >= 4 weeks)	CR
	CR + (T2-T1 < 4 weeks)	SD if T2 >= 6 weeks, otherwise NE
	PR	SD if T1 >= 6 weeks, otherwise PD
	SD	If T1 >= 6 weeks, SD; otherwise, PD
	PD	If T1 >= 6 weeks, SD; otherwise, PD
	NE, unknown or missing	SD if T1 >= 6 weeks, otherwise NE
PR	CR + (T2-T1 >= 4 weeks)	PR
	CR + (T2-T1 < 4 weeks)	SD if T2 >= 6 weeks; otherwise NE
	PR + (T2-T1 >= 4 weeks)	PR
	PR + (T2-T1 < 4 weeks)	SD if T2 >= 6 weeks, otherwise NE
	SD	SD if T2 >= 6 weeks, otherwise NE
	PD	SD if T1 >= 6 weeks, otherwise PD
	NE, unknown or missing	SD if T1 >= 6 weeks, otherwise NE
SD	CR，PR，SD	SD if T2 >= 6 weeks, otherwise NE
	PD, death due to PD	If T1 >= 6 weeks, SD; otherwise, PD
	NE, unknown or missing	SD if T1 >= 6 weeks, otherwise NE
PD	Any other	PD
NE	NE, unknown or missing	NE

Notes:

1. CR is complete response, PR is partial response, SD is stable disease, PD is Disease progression, and NE is non-evaluable.
2. T1: Time interval from the first infusion to the time point for evaluation of overall response
3. T2: Interval between the first infusion and the subsequent time point for which the response is to be confirmed for the evaluation of overall response. When the same evaluation result of tumor is obtained consecutively for multiple times after the time point for which the response is to be confirmed, T2 is the interval between the first infusion and the time point for which the evaluation of overall response is to be confirmed for the last overall response.

5.9.2 Time to event

Progression-free survival (PFS), duration of response (DOR), and overall survival (OS) will be calculated. Survival functions will be estimated using the Kaplan-Meier nonparametric maximum likelihood method and survival curves will be plotted. See

Table 3 for criteria for determination of events and censored times. Median, 25th and 75th percentiles of PFS, DOR and OS will be estimated using the Kaplan-Meier method, and corresponding two-sided progressive 95% confidence intervals will be calculated using the Brookmeyer-Crowley method. Using the Kaplan Meier method, the OS rate at 1 year after the first dose will be estimated and the 95% CI will be calculated using the standard error calculated using the Greenwood formula. If data do not allow for an analysis, the results of the analysis will be reported as NA.

Tumor time event list.

Table 3 Judgment Criteria for Event and Censoring Time

Condition	**Event or censoring time**	**Events/ Censored**	**Applicable Endpoints**
Incomplete or no baseline tumor evaluation	Date of enrollment	Censored	PFS
No disease progression or death, and no prohibited antitumor therapy	Time of the last assessment visit (exclude the visit date when the assessment result is not estimable (NE))	Censored	DOR PFS
Missing post-baseline evaluation and death prior to the first scheduled tumor assessment	Date of death	Events	PFS
No tumor assessment after baseline and no death	Date of enrollment	Censored	PFS
Progression or death after <=1 missing post-baseline tumor assessment, before receiving new anti-tumor treatment	Time to disease progression or death	Event	DOR PFS
Progressive disease or death after 2 or more times* tumor assessment	Time of the last assessment prior to death or disease progression (not including the time of assessment with NE results)	Censored	DOR PFS
No Tumour progression, no death, and no new antitumor treatment	Date of the last assessment prior to receiving prohibited antitumor therapy	Censored	DOR PFS

	(not including the visit date when the evaluation result is not available)		

* See Appendix

5.10 Pharmacokinetic analysis

Pharmacokinetic concentration analysis: the pharmacokinetic concentrations of Toripalimab and cetuximab were analyzed descriptively, and the statistics included number of cases, arithmetic mean, standard deviation, Variable Coefficient, geometric mean, geometric Variable Coefficient, median, minimum and maximum. The individual pharmacokinetic time-course was plotted according to the actual sampling time. The average pharmacokinetic time-course was plotted using the planned sampling time (mean ± standard deviation, linear coordinates). In the linear coordinates, BQL before Tmax was processed as 0, and BQL after Tmax was processed as missing.

Pharmacokinetic parameter analysis: Clinical pharmacologists will calculate the PK parameters of toripalimab and cetuximab with non-compartmental model (NCA) using Phoenix WinNonlin software. The parameters were calculated using actual sampling times. Descriptive statistics were performed for pharmacokinetic parameters of toripalimab and cetuximab. The statistics included number of cases, arithmetic mean, standard deviation, Variable Coefficient, geometric mean, geometric Variable Coefficient, median, minimum, and maximum.

5.11 Immunogenicity Analysis

Descriptive statistics were used to analyze the changes in the generation of anti-terraplilumab antibody and anti-cetuximab antibody at each sampling timepoint after treatment. The number and percentage of baseline or postbaseline ADA-positive patients, and baseline ADA-positive/negative patients and treatment-related ADA-positive patients were summarized.

Treatment-related ADA positive subjects referred to subjects with immunogenicity positive samples after baseline. Mainly included:

- Treatment-induced ADA positive: subjects who were ADA negative in the baseline sample and became ADA positive after baseline.
- Treatment-emergent ADA positive: baseline sample is ADA positive, and

postbaseline sample is ADA positive with an antibody titer ≥ 4× (toripalimab) / 9× (cetuximab) of the baseline ADA positive sample.

For treatment-related ADA positive subjects, the onset time was calculated.

An ADA-negative subject is defined as having no treatment-induced or treatment-enhanced Antibody positive samples during treatment or follow-up.

At the same time, a summary analysis will be performed for the incidence of Neutralising antibodies positive. As long as a positive test result of Neutralising antibodies is present at the visit, the subject is considered to be Neutralising antibodies positive. If the subject does not have a positive Antibody test result, Neutralising antibodies test will not be performed, i.e., the test result of Neutralising antibodies is negative.

Immunogenicity data will be tabulated. The titer will be plotted as mean-time curve and median-time curve for the subjects with positive ADA, according to the scheduled sampling timepoints.

5.12 Exploratory Analysis

iORR, iDCR, iDOR, and iPFS assessed according to iRECIST.

For iDOR and iPFS, Kaplan-Meier nonparametric maximum likelihood method is used to estimate survival functions, and survival curves are plotted. Median, 25th and 75th percentiles of iDOR and iPFS are estimated using Kaplan-Meier method, and the corresponding two-sided asymptotic 95% confidence intervals are calculated using the Brookmeyer-Crowley method.

Number and percentage of patients with iORR and iDCR, as well as the Clopper-Pearson exact method to construct the two sided 95% confidence interval were calculated.

Patient biomarker results will be summarized, including PD-L1 staining TC, staining score, combined positive score CPS, combined positive score CPS score, and qualitative results. HPV16 test results for patients with oropharyngeal cancer will be summarized by central laboratory, previous test results, and overall test results.

Draw a forest plot of ORR based on biomarkers. Compare the hazard ratios between different levels of the same biomarker using a COX regression model.

6 APPENDICES

6.1 Appendix 1: Principles for Handling Missing Data and Imputation Rules

Basic rules

Missing start date of event	**Imputation rule**
Missing year, month, day	Missingness flag maintained
Missing month and day	Use January 1 to fill in the missing month and date
Missing date	Day was imputed with 1 day.
Missing end date of the event	**Fill-in rules**
Missing year, month, day	Missingness by design
Missing month and day	Use December 31 to impute missing month, day, and year
Missing date	Use the last day of the known month to impute missing days

Note:

a. For deceased subjects, the imputed date cannot be later than the date of death.

b. For subjects who did not die, the imputed date cannot be later than the last known date of survival

If the start/end date is completely missing, DM should confirm

Additional rules:

1 Missing birth date

Missing birth date	**Imputation rule**
Missing year, month, day	Missingness flag maintained
Missing month and day	Use July 1 to fill in the missing month and date
Missing date	Missing days were imputed with 15 days.

2 Tumor diagnosis: If the date of first diagnosis/current diagnosis/first recurrence of disease is missing, please refer to the filling rules for the start date of event in Part 1;

for the last treatment date, please refer to the filling rules for the end date of event in Part 1.

3 The missing start/end dates for prior non-anti-tumor medication, concomitant medication, prior non-anti-tumor non-drug therapy/operation, concomitant non-drug therapy/operation, and prior/concomitant disease history will not be imputed. If it cannot be judged by the available information, the medication or treatment will be judged as a concomitant medication or treatment.

4 Missing date for AE

Missing start date	**Imputation rule**
Missing year, month, day	If the end date of AE was earlier than the date of the first dose, the start date of AE remained missing and was counted as a non-TEAE; otherwise, the date of the first dose was used as the start date of AE and was counted as a TEAE.
Missing month and day	1，If the year is the same as the year of the first dosing date, then the start date of the AE is the same as the first dosing date. 2，If the year was not equal to the year in which the first dose was taken, then 1 January was used for imputation.
Missing date	1，If the year and month were the same as that of the date of the first dose, the start date of the AE was the date of the first dose. 2，If the year and month were not equal to those of the date of the first dose, the first day of the known month was used for imputation.
End date is missing	**Imputation rule**
Missing year, month, day	Missing.
Missing month and day	Use December 31 to impute missing month, day, and year.
Missing date	Impute with the last day of the month.

Note: 1. If the completed start date was after the end date, the end date was used as the corresponding start date. 2. If the AE start and end dates were missing after DM confirmation, they were counted as TEAEs.

5 Missing date for subsequent antitumor therapy

Missing start date	**Fill-in rules**
Missing year, month, day	Missingness flag maintained
Missing month and day	Missingness flag maintained
Missing date	1. If the year and month were the same as the year and month of the last dose, then the date of the last study dose or the end date of the subsequent antitumor therapy was used for imputation (whichever came first). 2. If the year and month were different from those of the last dosing date, the missing date was filled with 1 day.
End date is missing	**Not imputed**

6 Missing date of death should not be allowed, and no imputation is needed.

If the data is still missing after all efforts, the following rules can be referred to, and the final rules can be determined after discussion with the statistician:

Missing date of death	**Imputation rule**
Missing year, month, day	Missingness maintained. OS is missing at the last known alive date.

Missing month and day	Missingness maintained. OS is missing at the last known alive date.
Missing date	The date of death was replaced by the first day of the month of that year, and the subject died on the date of replacement, i.e., an OS event. NOTE: If the imputed date of death is earlier than or equal to the last known alive date, the imputed date of death will be updated with the last known alive date + 1.

7 Lab test values recorded as below (and equal to) or above (and equal to) the test range value (e.g., <x, ≤x, >x, ≥x) will be treated as the test range value (i.e., =x) when summarizing descriptive statistics, but will still be listed as "<x", "≤x", ">x", or "≥x" in the data listings.

6.2 Appendix 2: Mapping Rules for Tumor Assessment Periods

Tumor Assessment Cycle	Target Day	SCOPE
Week 7	43	< 64
Week 13	85	64=<, <106
Week 19	127	106=<, <148
Week 25	169	148=<, <190
Week 31	211	190=<, <232
Week 37	253	232=<, <274
Week 43	295	274=<, <316
Week 49	337	316=<, <368
Week 58	400	368=<, <431
Week 67	463	431=<, <494
Week 76	526	494=<, <557
Week 85	589	557=<, <620
Week 94	652	620=<, <683

Note that tumor evaluation will be performed every 6 weeks in the first year and every 9 weeks thereafter. If the actual tumor evaluation cycle is longer than the above time, it should be extended according to the same rule.