# Clinical Study Protocol

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| **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** |
| **Study Number:** | **JS001-037-Ib/II-HNSCC** |
| **Generic Name of the Study Drug:** | **Toripalimab Injection (JS001)** |
| **Study Phase** | **Ib/II** |
| **Sponsor:** | **Shanghai Junshi Biosciences Co., Ltd.**<br>**Suzhou Zhonghe Biomedical Technology Co., Ltd.** |
| **Principal Investigator:** | **Prof. Ye Guo** |
| **Leading Institution of the Study** | **Shanghai East Hospital** |
| **Version No. and Date:** | **4.0, September 13, 2024** |

# Signature Page

## Principal Investigator

I have read the clinical study protocol for "A Single Arm, Multi-Center, Phase 1b/2 Clinical Study of Toripalimab (JS001) in Combination with Cetuximab for the Treatment of Advanced Squamous Cell Carcinoma of Head and Neck" (Protocol No.: JS001-037-Ib/II-HNSCC, Version No.: 4.0, Version Date: September 13, 2024), and I agree to conduct this clinical trial in strict accordance with the protocol, Good Clinical Practice (GCP), and all currently applicable regulations, as well as the Declaration of Helsinki. I will provide a copy of the protocol to my research team and discuss it with them to ensure that they have a full understanding of this trial.

I agree that the confidential information contained in this document shall not be used for other purposes other than the evaluation or conduction of the clinical study, without prior written approval by Shanghai Junshi Biosciences Co., Ltd.

Study Institution:

| | | |
|---|---|---|
| Principal Investigator (print name) | Principal Investigator (Signature) | Date (Day/Month/Year) |

## Sponsor's Medical Responsible Person

I have read and confirm this clinical study protocol (Protocol No.: JS001-037-Ib/II-HNSCC, Version No.: 4.0, Version Date: September 13, 2024). I agree to perform the relevant responsibilities in accordance with Chinese laws, the Declaration of Helsinki, Good Clinical Practice (GCP), and this study protocol.

Sponsor: Shanghai Junshi Biosciences Co., Ltd.

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|---|---|---|
| Medical Responsible Person (print name) | Medical Responsible Person (signature) | Date (Day/Month/Year) |

# Study Protocol Revision History

| **DOCUMENT HISTORY** | |
|---|---|
| **Documentation** | **Date** |
| **Original protocol (1.0)** | **August 15, 2020** |
| **Protocol (2.0)** | **January 28, 2022** |
| **Protocol (3.0)** | **October 10, 2022** |
| **Protocol (4.0)** | **September 13, 2024** |

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# Abbreviations

| Abbreviations or Terms | Definition/Interpretation |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Events of special interest |
| AGC | Grailed leukocytes |
| aPTT | Activated Partial Thromboplastin Time |
| ALP | Alk phos |
| ALT | Alanine aminotransferase |
| ANC | Neutrophil count |
| ARDS | acute Respiratory distress syndrome |
| AST | Aspartate aminotransferase |
| ADA | Anti-drug Antibody |
| AUC | Area under the concentration-time curve |
| $AUC_{0-\infty}$ | Area under the plasma drug concentration-time curve from time 0 to infinite time (∞) |
| $AUC_{0-t}$ | Area under the plasma concentration-time curve from time 0 to the last timepoint at which a plasma concentration can be determined with accuracy |
| BSA | Body surface area |
| NMPA | National Medical Products Administration |
| CI | Confidence interval |
| $C_{max}$ | Peak concentration |
| CNS | Central Nervous System |
| CPS | Positive combined score |
| CR | Complete Response |
| CrCL | Creatinine clearance |
| CT | Computerised tomography |
| CTCAE | Common Adverse Reaction Evaluation Criteria |
| CTL | Cytotoxic T Lymphocytes |
| DCR | Disease control rate |
| DLT | Dose-limiting toxicity |
| DNA | Deoxyribonucleic Acid |
| DOR | Duration of Response |
| EBV | Epstein-Barr virus |
| EC | Ethic Committee |
| ECG | Electrocardiogram |

| | |
|---|---|
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EGFR | Epidermal Growth Factor Receptor |
| EORTC | European Organisation for Research and Treatment of Cancer |
| FDA | Food and Drug Administration |
| FFPE | Fixation with formalin and paraffin embedding |
| FT3 | Tri-iodothyronine free |
| FT4 | Thyroxine free |
| G-CSF | Granulocyte Colony-Stimulating Factor |
| GCP | Good Clinical Practice |
| HBcAb | HBsAcg |
| HBeAb | HBeAb |
| HBeAg | HBeAg |
| HBsAb | HBsAb |
| HBsAg | HBsAg |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HER-2 | Human growth epidermal factor receptor-2 |
| HIV | Human Immunodeficiency Virus |
| HNSCC | Squamous cell carcinoma of head and neck |
| HPV | Human papillomavirus |
| HR | Hazard ratio |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IFN | Interferon |
| IHC | Immunohistochemistry |
| IRC | Independent Review Committee |
| INR | International normalised ratio |
| irAE | Immune-related Adverse Event |
| iRECIST | Modified Immune-related Response Criteria for Solid tumour |
| ITT | Intent-to-Treat |
| IxRS | Interactive Voice Response System/Interactive Web Response System |
| LPLV | Last Patient Last Visit |
| MRI | Magnetic resonance imaging |

| | |
|---|---|
| MTD | Maximum Tolerated Dose |
| NGS | Next-generation sequencing |
| NIAID | National Institute of Allergy and Infectious Diseases, USA |
| NOAEL | No Observed Adverse Reaction Level |
| NSAID | Non-steroidal anti-inflammatory drug |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PCR | Polymerase chain reaction |
| PD-1 | Programmed death receptor-1 |
| PD-L1 | Programmed death ligand-1 |
| PEF | Peak expiratory flow |
| PFS | Progression-free survival |
| PK | Pharmacokinetics |
| PR | Partial Response |
| PRO | patient-REPORTED OUTCOMES |
| PT | Preferred Term |
| QW | Once a week |
| Q3W | Every 3 weeks |
| qRT-PCR | quantitative Reverse-Transcriptase-Polymerase Chain Reaction |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | Ribonucleic Acid |
| RP2D | Phase II recommended dose |
| SAE | Serious Adverse Event |
| SoA | Study Schedule Form |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| $t_{1/2}$ | Half-life |
| TBNK | Lymphocyte subgroups |
| TIL | Tumor invasion Lymphocytes |
| TKI | Tyrosine kinase inhibitors |
| $T_{max}$ | Time to peak |
| TNF | Tumour necrosis factor |
| TSH | Thyroid stimulating hormone |
| T3 | Total tri-iodothyronine |
| T4 | Total Thyroxine |

| | |
|---|---|
| TTD | Time to Exacerbation |
| TTR | Time to response |
| ULN | Upper limit of normal |
| VEGF | vascular Endothelial Growth Factor |
| WES | whole-EXOME SEQUENCING |

# 1 SYNOPSIS OF THE STUDY PROTOCOL

## 1.1 Synopsis

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|---|---|
| **Study Protocol 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 |
| **Generic Name of the Study Drug:** | Toripalimab Injection (JS001) |
| **Study Number:** | JS001-037-Ib/II-HNSCC |
| **Study Phase:** | Ib/II |
| **Indications:** | Cohort A: Recurrent or metastatic squamous cell carcinoma of head and neck (HNSCC) after treatment failure of a first-line platinum-based regimen<br><br>Cohort B: Patients with HNSCC who have not received systemic therapy for recurrence or metastatic disease and who are determined by a central Lab test to have positive PD-L1 expression |
| **Study Objectives** | |
| ◆ Phase Ib study:<br><br>Primary Objectives:<br><br>· To evaluate the safety and tolerability of toripalimab combined with cetuximab (hereinafter referred to as the "combination regimen") in patients with recurrent or mtastatic HNSCC.<br><br>Secondary Objectives:<br><br>· To determine the recommended phase 2 dose (RP2D) of the combination regimen in patients with recurrent or metastatic HNSCC.<br><br>· To evaluate the pharmacokinetic (PK) profile of the combination regimen in patients with recurrent or metastatic HNSCC.<br><br>· To evaluate the efficacy of the combination regimen in the treatment of recurrent or metastatic HNSCC. | |

◆ Phase II study:

Primary Objectives:

· 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 tumour version 1.1 (RECIST 1.1).

Secondary Objectives:

· To evaluate the efficacy of 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 using overall survival (OS) and 1-year OS rate.

· To further evaluate the safety and tolerability of the combination regimen in patients with recurrent or metastatic HNSCC.

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

· To evaluate the efficacy of the combination regimen in patients with recurrent or metastatic HNSCC using Immune-related Response Evaluation Criteria in Solid tumour (iRECIST).

· Test biomarkers and evaluate their relationship with efficacy.

· To evaluate the immunogenicity of JS001 and cetuximab.

**Study Endpoints**

◆ Phase Ib study:

Primary Study Endpoints:

• 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.

Secondary Endpoints:

• 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 the IRC and the study investigators according to RECIST 1.1

- OS and 1-year OS rate.

◆ Phase II study:

Primary Study Endpoints:

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

Secondary Endpoints:

- 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 as 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.

◆ Exploratory study endpoints (applicable to Ib and phase II study):

- 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.
- Immunogenicity of JS001 and anti-cetuximab ，evaluate the correlation with PK parameters, safety and efficacy data.

**Overall design:**

This is an open-label, multi-center Phase Ib/II clinical study. The Phase Ib study is mainly 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 is divided into two cohorts, i.e.,

cohort A is mainly 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 mainly used to evaluate the efficacy and safety of the combination regimen in the treatment of PD-L1-positive HNSCC without previous systemic therapy for recurrents or metastatic disease.

The study includes a screening period, a treatment period and a follow-up period. The screening period is no longer than 28 days. After completion of the screening period examinations and assessments, eligible patients will enter the study treatment period. Patients should receive study treatment as specified in the protocol until disease progression by radiological criteria according to RECIST 1.1, intolerable toxicity, patient request to discontinue study treatment or withdraw informed consent, or investigator's judgment that treatment withdrawal is necessary, or up to 2 years of treatment (whichever occurs first).

Safety data were collected continuously during the study. The incidence and severity of Adverse Events were assessed for safety and tolerability according to the NCI-CTCAE v5.0 criteria. Laboratory tests, vital signs, ECOG performance status, Physical examination, ECG, and Adverse Events were assessed continuously during the trial.

Tumor evaluation was performed at screening (as baseline), every 6 weeks (±7 days) within the first 12 months, and every 9 weeks (±7 days) thereafter until radiographic documentation of disease progression (PD), iCPD judged by the investigator (for subjects with the first radiographic presentation of PD but judged by the investigator to be able to continue treatment), withdrawal of informed consent, loss to follow-up, initiation of new anti-tumor therapy, or termination of the study. Subjects who drop out of the study for reasons other than non-disease progression (including drop out due to AEs or treatment interval out of window), and do not experience disease progression at the time of drop out, will continue to undergo radiographic evaluation until disease progression, death, loss to follow-up, or initiation of new anti-tumor therapy. The management of the subject's treatment will be based on the tumor evaluation results of the investigator.

For patients who present with disease progression on imaging according to RECIST1.1, the treatment can be continued as long as the investigator judges that the patient can still benefit from the drug treatment and after discussion with the medical monitorof the sponsor. The clinical benefit is evaluated by the investigator based on the iRECIST, taking into account the imaging findings and clinical condition, in the absence of intolerable toxicity or worsening of symptoms due to disease progression.

All subjects should have immunogenicity blood samples and pharmacokinetic blood samples collected according to the protocol for corresponding immunogenicity and pharmacokinetic analysis. In addition to the subjects in Phase II Cohort B who must provide a qualified tumor tissue sample for PD-L1 testing, all subjects must also provide a qualified tumor tissue sample. Subjects who are unable to provide a qualified tumor tissue sample may also be enrolled after discussion and agreement between the investigator and the Sponsor.

◆ Phase Ib study

A cycle consists of 21 days. Toripalimab will be administered on Day 1 of each cycle, followed by observation for approximately 60 minutes, and then cetuximab will be administered. The specific dosing regimen is provided in the table below:

| **Dose group** | **Investigational product** | **Every cycle (21 days)** | | |
|---|---|---|---|---|
| | | **Day 1** | **Day 8** | **Day 15** |
| **Initial dose group** | Toripalimab | 240mg | / | / |
| | Cetuximab | 400 mg/m$^2$ in the first cycle<br>250 mg/m$^2$ in subsequent cycles | 250mg/m$^2$ | 250mg/m$^2$ |
| **alternate dose group** | Toripalimab | 240mg | / | / |
| | Cetuximab | Cycle 1: 400 mg/m$^2$<br>200 mg/m$^2$ in subsequent cycles | 200mg/m$^2$ | 200mg/m$^2$ |

First, 6 patients were enrolled to receive the initial dose as the tolerability observation period of the first dosing cycle (21 days). If <2 patients developed dose-limiting toxicity (DLT), then 6 patients were enrolled (total 12 patients) to collect adequate safety and PK data of the

combination therapy. The SMC determined whether the dose could be used as the recommended dose for phase II based on the safety and PK data of 12 patients.

If DLT occurs in ≥2 patients in the first 6 patients, the dose will be adjusted to the alternative dose and enrollment and observation will be performed according to the above enrollment plan. If DLT occurs in ≥2 patients in the first 6 patients in the alternative dose group, SMC will decide whether to use other dose levels/dose cycles for the study based on the available safety and PK data.

If a patient is discontinued from the study due to a non-drug-related Adverse Event or an Adverse Event that does not meet the criteria for dose interruption/reduction, and the actual dose of toripalimab or cetuximab in the first cycle is less than 80% of the expected dose, the patient will be replaced after discussion and agreement by SMC.

- Phase II study

Patients who participate in the phase II study will receive toripalimab in combination with cetuximab at the RP2D established in the phase Ib study. Treatment will continue until disease progression by RECIST 1.1, intolerable toxicity, withdrawal of consent, or investigator's decision for treatment withdrawal, or up to 2 years of treatment, whichever comes 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.

**Inclusion/exclusion criteria**

Inclusion Criteria

Patients must meet all of the following inclusion criteria to be enrolled in this study:

1. Patients who are willing to participate in this study and sign the informed consent form on a voluntary basis after adequate informed consent;
2. Aged ≥18 and ≤75 at time of signing ICF;
3. Histologically or cytologically confirmed advanced, recurrent, or metastatic head and neck squamous cell carcinoma originating in the oral cavity, oropharynx, hypopharynx, larynx, or paranasal sinuses, not amenable to local treatments such as surgery or radiotherapy;
4. Ib cohort A: patients who have received first-line platinum-based chemotherapy for recurrent and metastatic disease and developed progressive disease during or after treatment, or have received a platinum-based regimen as neoadjuvant or adjuvant chemotherapy (or Radiochemotherapy) and developed recurrence or metastatic disease within 6 months after treatment completion.
5. Phase II Cohort B:

   1) No previous systemic therapy for recurrent or metastatic disease. If previous systemic therapy was used as part of local therapy, recurrence or metastasis occurred more than 6 months after the end of treatment.

   2) Patients must provide a qualified tumor tissue sample and PD-L1 expression is positive as determined by central Lab test (positive definition as Combined Positive Score (CPS) ≥ 1).
6. All acute toxicities resulting from prior anticancer therapy, surgery, or radiotherapy must have resolved to Grade 0-1 (per NCI-CTCAE v5.0) or to the level specified in the inclusion/exclusion criteria. Exceptions include alopecia, pigmentation, or other toxicities deemed by the investigator to pose no safety risk to the subject and not affecting treatment compliance.
7. An archival tumor specimen or fresh tumor biopsy sample is available.
8. For subjects with Oropharyngeal cancer, a report of prior HPV16 test or qualified tumor

tissue samples for HPV status test can be provided.

9. At least one measurable lesion according to RECIST 1.1;
10. Expected survival ≥12 weeks;
11. Eastern Cooperative Collaboration Oncology Group (ECOG) performance status score of 0 or 1;
12. Adequate organ function:

| System Organ | Lab values |
|---|---|
| **Hematology (no history of transfusion or colony-stimulating factor or other drugs used for correction within 14 days prior to the first dose of study drug)** | |
| Neutrophil count | ≥$1.5\times10^9$/L |
| Platelet count | ≥$100\times10^9$/ L |
| Haemoglobin | ≥90 g/L |
| **Renal Function** | |
| Serum creatinine or | ≤ 1.5 × upper limit of normal (ULN) |
| Creatinine clearance calculated using the Cockcroft-Gault formula or center practice | ≥50 mL/min |
| **Liver function** | |
| Bilirubin total | ≤ 1.5 × ULN or<br>≤ 3 ULN (patients with known Gilbert's disease) |
| ALT/AST | ≤ 3 ULN (no metastases to liver)<br>≤5 ULN in presence of metastases to liver |
| Albumin (no infusion of albumin preparations within 14 days prior to the first dose of the study drug) | ≥30 g/L |
| **Coagulation function** | |
| International normalized ratio (INR)<br>Prothrombin time (PT)<br>Activated partial thromboplastin time (aPTT) | ≤ 1.5 × ULN |

13. Females of childbearing potential must confirm a negative serum pregnancy test within 72 hours prior to the first dose and agree to use effective contraception during study drug use and for 5 months after the last dose. In this protocol, a female of childbearing potential is defined as:

    1) Have not undergone amputation of uterus or bilateral oophorectomy,

2）Natural menopause for no consecutive 24 months (cessation of menstruation after cancer treatment does not exclude fertility) (i.e., having menstruated at any time in the previous consecutive 24 months).

Male patients with sexual partners of childbearing age must agree to use effective contraception during the use of the study drug and for 5 months after the last dose.

• Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Histologically or cytologically confirmed nasopharyngeal cancer, salivary gland carcinoma, or other non-squamous cell carcinoma (e.g., adenocarcinoma, sarcoma, or mixed carcinoma), and metastatic squamous cell carcinoma of unknown primary site.
2. Presence of necrotic lesions with risk of Major bleed as assessed by the investigator.
3. Previous treatment with other immune checkpoint inhibitors/agents targeting the immune checkpoint pathway/other agents that target T cell co-stimulation (e.g., PD-1/PD-L1 antibody or CTLA-4 antibody);
4. Previously treated with EGFR inhibitors (including radiotherapy sensitizers).
5. Diagnosis of other neoplasm malignant within 5 years prior to entry, except for skin basal cell carcinoma or squamous cell carcinoma that has been cured by local treatment, superficial bladder cancer, carcinoma cervix in situ, or carcinoma in situ of breast ductal.
6. Uncontrollable or symptomatic active central nervous system (CNS) metastasis, which may present as clinical symptoms, brain oedema, spinal cord compression, carcinomatous meningitis, leptomeningeal disease and/or progressive growth;
   1) Imaging findings indicating asymptomatic spinal cord compression that has been assessed by a specialist as stable and does not currently require intervention are excluded;
   2) Excluded are patients who have received treatment for CNS metastases and have demonstrated radiographic stability for ≥4 weeks during the screening period, and have discontinued systemic corticosteroid therapy at a dose >10 mg/day of prednisone or equivalent for ≥4 weeks prior to the first study dose;

7. Poorly controlled Pleural effusion, peritoneal, or Pericardial effusion;
8. Having Grade ≥2 Neuropathy peripheral (per NCI-CTCAE 5.0) or hearing loss;
9. Female patients who are pregnant or breastfeeding;
10. Occurrence of any of the following within 6 months prior to the first study dose: myocardial infarction, severe/unstable angina, cardiac dysfunction of NYHA Class II or higher, clinically significant supraventricular or ventricular arrhythmias, and symptomatic congestive heart failure;

    Note: Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on an optimized and stable medical regimen as determined by the treating physician, in consultation with a cardiologist if appropriate;
11. Poorly controlled Hypertension (Blood pressure systolic ≥160 mmHg and/or Blood pressure diastolic ≥100 mmHg) (based on the average of ≥3 BP readings obtained from ≥2 measurements); Hypertensive crisis or hypertensive encephalopathy within 6 months of the first dose;
12. Known allergy to the investigational drug or any of its excipients, or a history of serious allergic reaction to other monoclonal antibodies;
13. Prior use of the following medications or drug therapy prior to the first dose of study drug:
    1) Major surgery within 28 days prior to the first dose of study treatment (tissue biopsy performed for diagnostic purposes and central venous catheterization (PICC) or infusion port implantation through peripheral venous puncture are allowed).
    2) Have received any anti-tumor therapy (including chemotherapy, radiotherapy, immunotherapy, endocrine therapy, targeted therapy, cytokine therapy or biological therapy) within 28 days prior to the first study medication;
    3) Participated in other intervention studies within 28 weeks prior to the first dose of study drug;
    4) Received systemic immunomodulatory agents (including but not limited to interferon or IL-2) within 14 days prior to the first study dose or 5 half-lives of the drug, whichever is longer;
    5) Have received systemic corticosteroids (>10 mg/day prednisone or equivalent) or

other systemic immunosuppressive agents (including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumour necrosis [anti-TNF] drugs) within 14 days prior to the first study dose;

- Topical, ophthalmic, intra-articular, intranasal, and inhaled corticosteroids were allowed;
- Patients receiving acute low-dose systemic immunosuppressive agents (such as treatment of nausea with a single dose of dexamethasone, or premedication for cetuximab) can discuss with the medical monitor and obtain approval to be enrolled in the study;
- Patients who have had previous allergic reactions to intravenous contrast for MRI/CT tumor evaluation at baseline and subsequent tumor assessments may receive preventive use of steroid;
- Inhaled corticosteroids are allowed for treatment of chronic obstructive pulmonary disease, hydrocortisone (e.g., fludrocortisone) for treatment of patients with Orthostatic hypotension, and low-dose corticosteroids for maintenance treatment of adrenal cortex insufficiency;

6) Received oral or intravenous antibiotic therapy within 14 days prior to the first dose of study drug (except for prophylactic antibiotic therapy);
7) Vaccination with any live vaccine (e.g., vaccine against infectious diseases, such as influenza vaccine, varicella vaccine, etc.) within 28 days prior to the first study dose;

14. History of autoimmune disease, including but not limited to Myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sicca syndrome, Guillain-Barre syndrome, multiple sclerosis, vasculitis or glomerulonephritis;
    1) Patients with thyroid function decreased who are receiving stable doses of thyroid hormone replacement therapy are eligible to participate in this study;
    2) Patients with type I Diabetes mellitus under stable Insulin regimen who have controlled disease are eligible to participate in this study;
15. History of allogeneic organ transplant or allogeneic hematopoietic stem cell transplant;

16. Any serious infection (NCI-CTCAE > grade 2) within 28 days prior to the first dose of study drug, e.g., severe pneumonia, bacteraemia, and infections with complications requiring hospitalisation.
17. Active infection, including but not limited to tuberculosis (clinical diagnosis includes clinical history, physical examination and radiological findings, as well as TB examination according to local medical routine), hepatitis B, hepatitis C or human immunodeficiency virus (HIV antibody positive);
    1) Patients who are positive for hepatitis B surface antigen (HBsAg+) and/or hepatitis B core antibody positive (HBcAb+) need to undergo hepatitis B virus deoxyribonucleic acid (HBV DNA) test. If the HBV DNA copy number is <1000/mL, or <200IU/mL, or <lower limit of detection of the study center, they can participate in this study;
    2) Patients with Hepatitis C antibody positive (HCV Ab+) need to undergo HCV RNA test, and only those with negative HCV RNA (defined as below the lower limit of detection at the study center) are eligible for this study;
18. Idiopathic pulmonary fibrosis, drug-induced pneumonia, organising pneumonia (i.e., obliterative bronchiolitis), radiation pneumonitis with clinical symptoms or requiring steroid treatment, active pneumonia, or other moderate to severe lung disorders significantly affecting lung function.
19. Patients with other serious physical or mental diseases or laboratory test abnormalities, or those with alcoholism or Drug of Abuse, which may increase the risk of participation in the study, affect treatment compliance, or interfere with the study results, as well as patients who, in the judgment of the investigator, are not suitable for participation in this study.

**Intervention group and duration:**

Investigational Product, Dosage and Administration:

Study Drug 1: Toripalimab Injection (JS001)

Specification: 240 mg/6 mL/vial; sterile solution; shelf life: 24 months; storage condition: store at 2 ~ 8 °C, protect from light.

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| Administration method: JS001 (240 mg) was administered intravenously on Day 1 of each 3-week treatment cycle.<br>Study Drug 2: Cetuximab<br>Specification: 100mg/20ml/vial; sterile solution; shelf life: 48 months; storage condition: 2~8 °C, refrigeration.<br>Method of administration (initial dose group): intravenous infusion. The initial dose was 400 mg/$m^2$ based on body surface area, and subsequent doses were 250 mg/$m^2$ based on body surface area, once a week (Days 1, 8, and 15).<br>Note: Dose adjustment may be made based on the Phase Ib safety and PK data after discussion by SMC.<br>Administration sequence: On Day 1 of each cycle, JS001 is administered first, followed by observation for about 60 min, and then cetuximab is administered. |
| Duration of intervention: |
| Subjects will receive toripalimab in combination with cetuximab. Until radiographic disease progression according to RECIST 1.1, intolerable toxicity, the subject's request to discontinue study treatment or withdraw informed consent, investigator judgment that treatment withdrawal should occur, or a maximum of 2 years of treatment (whichever occurs first). |

**Pharmacokinetic Evaluation**

- The blood collection time points for subjects participating in the phase Ib study are as follows:

The concentrations of cetuximab and JS001 were determined within 0.5 h before administration of Cycle 1 and Cycle 3 D1, immediately after the end of administration of JS001 (within 10 min, only JS001 was determined), immediately after the end of administration of cetuximab (within 10 min), 2 h (±5 min), 6 h (±15 min), 24 h (±1 h), 48 h (±2 h), 96 h (±2 h), 168 h (±8 h, before the second administration of cetuximab) after the end of administration of JS001, 336 h (±12 h, before the third administration of cetuximab), 504 h (±24 h, before the next cycle administration), immediately after the end of administration of JS001 in Cycle 2 D1 (within 10 min, only JS001 was determined), and immediately after the end of administration of cetuximab (within 10 min).

4 mL of blood will be collected for each blood collection time point (only 2 mL of blood will be collected for JS001 blood collection time point). See the Laboratory Manual for specific handling.

**Immunogenicity Evaluation**

6 mL blood was collected at each blood collection point (3 ml if single drug was determined). Blood samples were collected before the first dose, before D1 administration in Cycle 2 and Cycle 4, once every 12 weeks within the first year and once every 24 weeks thereafter (on the day of administration, before administration) for determination of anti-drug antibody (ADA) and trough concentation of JS001 and cetuximab, until discontinuation of study drug or end of study (whichever comes first), to evaluate the potential relationship between immunogenicity and pharmacokinetics, safety and efficacy.

**Biomarker Evaluation**

Patients should provide tumor tissue samples. Fresh specimen (preferred) or formalin-fixed, paraffin-embedded tumor tissue blocks or unstained tumor specimen sections, at least 8 unstained sections (for patients with oropharyngeal cancer, if HPV16 test results are not available in the past, 2 additional sections are required). 2 mL of whole blood will also be collected for paired sequencing testing. Except for patients in Phase II Cohort B, who must provide a tumor tissue sample for PD-L1 testing, patients who cannot provide a tumor tissue sample may also be enrolled after discussion and agreement by the investigator and the sponsor. Tumor samples must have good quality in terms of tumor content and viable tumor tissue content. Cytological smears obtained by drainage of pleural effusion or tumor tissue from metastases to bone are not recommended. Samples should be sent to the central laboratory for testing of the following biomarkers:

- PD-L1 expression: the antibody used for PD-L1 detection was JS311, an anti-PD-L1 monoclonal antibody developed by Junshi.
- HPV 16 (applicable only to Oropharyngeal cancer)
- Tumor mutation burden (TMB): Tumor tissue will be tested using whole-exome sequencing (WES) technology to confirm the tumor mutation burden.

**Sample Size Determination**

The sample size for the Phase 1b study depends on the number of dose arms and the number of DLTs. A minimum of 12 patients will be enrolled to determine the recommended Phase II dose.

The sample size for the Phase II study was calculated based on the primary endpoint, objective response rate (ORR) evaluated according to RECIST version 1.1. The null hypothesis for cohort A was ORR = 20%. Assuming an ORR of 40% for toripalimab in combination with cetuximab, 24 patients were required to be enrolled in cohort A in Stage 1. If the number of

patients with response was less than or equal to 5, the cohort would be terminated. Otherwise, 21 additional patients were required to be enrolled to achieve a total of 45 patients. At a significance level of 0.05 (2-sided) and power of 90%, the null hypothesis would be rejected if the number of patients with response was greater than 13 in all patients. The null hypothesis for cohort B was ORR = 25%. Assuming an ORR of 43% for toripalimab in combination with cetuximab, 23 patients were required to be enrolled in cohort B in Stage 1. If the number of patients with response was less than or equal to 6, the cohort would be terminated. Otherwise, 20 additional patients were required to be enrolled to achieve a total of 43 patients. At a significance level of 0.05 (2-sided) and power of 80%, the null hypothesis would be rejected if the number of patients with response was greater than 15 in all patients.

**Statistical Methods**

**Analysis Sets**

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

The safety analysis set (SS) included all patients who received any dose of toripalimab. SS was the primary analysis set for safety, immunogenicity, pharmacokinetic, and biomarker analyses.

Efficacy evaluable analysis set (EAS) includes patients who have received at least one dose of toripalimab injection and have baseline tumor evaluation data and at least one post-treatment tumor evaluation data.

PK analysis set: includes all subjects who have received at least one dose and have at least one valid PK evaluation data.

**Efficacy analysis**

ORR and DCR will be calculated and 95% confidence intervals will be estimated using the Clopper-Pearson method.

The Kaplan-Meier method is used to calculate median DoR and PFS, and the Brookmeyer-Crowley method with log-log function transformation to normal approximation is used to estimate the 95% CI. The Kaplan-Meier method is used to estimate the 1-year OS rate, and the 95% confidence interval is estimated using the Greenwood formula.

**Safety analysis**

Safety analysis will be conducted on the safety analysis set. For the Phase Ib part, safety analysis will be conducted by different dose groups (if dose adjustment is made to the alternative dose group).

The extent of exposure to each study drug was summarized and described based on the number of cycles of treatment received (number and percentage of patients), duration of administration (days), cumulative total dose received by each patient (mg), dose intensity, and relative dose intensity.

Adverse Events will be coded and categorized using MedDRA22.1 or above. The number and incidence of treatment-emergent adverse events (TEAEs) will be tabulated by preferred term and system organ class. In addition, serious adverse events, adverse events of grade 3 and above, adverse events related to the study drug, and adverse events leading to discontinuation or interruption of the study drug will be summarized accordingly. Multiple occurrences of the same adverse event will be counted once according to the maximum severity. The above adverse events will be tabulated.

Deaths reported during study treatment and those reported during follow-up after treatment withdrawal will be summarized.

Descriptive statistics were used to summarize the measurements and changes from baseline at baseline and the last visit of the treatment period for Laboratory tests, Physical examination, vital signs, body weight, ECOG performance status, ECG, as well as the number

and proportion of patients with abnormal changes after baseline. The measurements at each visit were listed.

**PK analysis**

Based on the PK analysis set, PK concentration data were summarized and listed descriptively by drug at the protocol-specified time points. Mean and median drug concentration-time curves and semilogarithmic plots were plotted for each drug. Individual drug concentration-time curves and semilogarithmic plots were plotted for each subject according to actual sampling time. PK parameters of JS001 and cetuximab were calculated using the non-compartmental model in WinNonlin. Descriptive statistics were summarized and listed for plasma drug concentrations and PK parameters. If applicable, model-based methods will be used for exposure-response analysis.

| | |
|---|---|
| **Protocol Version and Date** | 4.0, September 13, 2024 |

## 1.2 Study Outline Act （SOA）

| | Screening Period | | Treatment Period [21] | | | Therapy cessation Visit [22] | Follow-up period | |
|---|---|---|---|---|---|---|---|---|
| | Day -28 to Day -1 | -7 to Day -1 | D1 | D8 | D15 | | Safety follow-up [23] | Survival follow-up [24] |
| **Visit window** | | | ± 3 days | ± 3 days | ± 3 days | ± 7 days | ± 7 days | ± 7 days |
| **Signing Informed Consent [1]** | × | | | | | | | |
| **Demographic data, height** | × | | | | | | | |
| **Previous medical history and treatment history [2]** | × | | | | | | | |
| **previously Reported HPV16** | × | | | | | | | |
| **Eligibility criteria check** | | × | | | | | | |
| **Body weight** | | × | × | × | × | × | | |
| **ECOG score** | | × | × | × | × | × | | |
| **Vital signs [3]** | | × | × | × | × | × | | |
| **Physical examination [4]** | | × | × | × | × | × | | |
| **12-lead Electrocardiogram [5]** | | × | × | | | × | | |
| **Echocardiogram [6]** | | × | | | | × | | |
| **Hematology [7]** | | × | × | | | × | | |
| **Blood chemistry [8]** | | × | × | | | × | | |
| **Coagulation tests [9]** | | × | × | | | × | | |
| **Urinalysis [10]** | | × | × | | | × | | |
| **Thyroid function [11]** | | × | × | | | × | | |
| **Virological test [12]** | × | | | | | | | |
| **Pregnancy test [13]** | | × | | | | × | | |
| **Tumor Imaging [14]** | × | | × | | | × | | × |
| **Tumor tissue sample [15]** | × | | | | | | | |
| **Pharmacokinetic blood collection [16]** | | | × | × | × | × | | |
| **Immunogenicity blood collection [17]** | | | × | ---------- | ---------- | × | | |
| **Investigational drug administration [18]** | | | × | × | × | | | |
| **Adverse Event [19]** | × | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | × |
| **Concomitant medication/treatment [20]** | × | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | × |
| **Subsequent anti-tumor therapy [25]** | | | | | | × | × | × |

Footnotes:

[1] Patients must sign the written informed consent form before screening procedures specified in this study can be performed. Prior to signing informed consent, tumor imaging and Laboratory test required for routine clinical care, and existing tumor tissue biopsy results, if within the specified window period, can be used.

[2] Medical history and treatment history: including tumor history (history of tumor diagnosis, surgery, radiotherapy, chemotherapy, etc.) and history of other concomitant diseases. Among them, the diagnosis of tumor should include: histological diagnosis results, histopathological typing, histological grading, clinical stage, and time of initial diagnosis before enrollment.

[3] Vital signs: pulse, respiratory rate, temperature, and blood pressure.
[4] Complete physical examination (general condition, head and face, skin, lymph nodes, eyes, ears, nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, nervous system and mental status, etc.) within 7 days before the first dose and at the therapy cessation visit; targeted physical examination before each dose and when clinically indicated.
[5] 12-lead Electrocardiogram: Prior to the first dose within 7 days, prior to dosing on Day 1 of each cycle (if Electrocardiogram is performed within 7 days prior to the first dose, there is no need to perform it again prior to the first dose), and at the Therapy cessation visit.
[6] Echocardiogram: performed within 7 days prior to the first dose and at the Therapy cessation visit, and as clinically indicated during the study.
[7] Hematology: Red blood cell count (RBC), haemoglobin (Hb), platelet count (PLT), white blood cell count (WBC), neutrophil count (ANC) and lymphocyte count, etc.; before the first dose within 7 days, before administration on Day 1 of each treatment cycle (if the screening test is completed within 7 days before the first dose, no retest is required before the first dose), and at the therapy cessation visit.
[8] Blood biochemistry: alanine transaminase (GPT), aspartate transaminase (Glutamic-oxaloacetic transferase), gamma-glutamyltransferase (γ-GT), total bilirubin (Bilirubin total), direct bilirubin (Bilirubin direct), alkaline phosphatase (Alk phos), blood urea nitrogen (BUN) or urea (BUN is preferred), protein total (Protein total), albumin (Albumin), creatinine (Cr), glucose (GLU), K+, Na+, Ca2+, Mg2+, Cl-; within 7 days before the first dose, before administration on Day 1 of each treatment cycle (if the screening test is completed within 7 days before the first dose, there is no need to repeat the test before the first dose) and at the therapy cessation visit.
[9] Coagulation function: activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), international normalized ratio (INR); within 7 days before the first dose, on the day before administration in each treatment cycle (if the screening test is completed within 7 days before the first dose, the test is not required again before the first dose), and at the Therapy cessation visit.
[10] Routine urine test: white blood cells, red blood cells, protein urine. It was performed within 7 days before the first dose, on the day 1 of each treatment cycle (if the screening tests were completed within 7 days before the first dose, the tests were not repeated before the first dose) and at the therapy cessation visit.
[11] Thyroid function: Serum thyroid stimulating hormone (TSH), free triiodothyronine (FT3), thyroxine free (FT4); if FT3 and FT4 are not available, T3 and T4 can be used instead; within 7 days before the first dose, before administration on Day 1 of each treatment cycle (if the screening period is completed within 7 days before the first dose, then no need to test again before the first dose), and at the therapy cessation visit.
[12] Virology test: HBsAg, HBsAb, HBeAg, HBeAb, HBcAb, HBV DNA (quantitative test of HBV DNA is required for patients with HBsAg+ and/or HBcAb+), HCV-Ab (quantitative test

of HCV-RNA is required if it is positive) and HIV-Ab. The test should be performed within 28 days prior to the first study treatment.

[13] Pregnancy test: It is applicable to women of childbearing age, using serum pregnancy test. It is performed within 72 hours before the first dose and at the Therapy cessation visit.

[14] Tumor imaging: enhanced CT or MRI of the head, neck, chest, and abdomen. Brain MRI is used for brain metastases that cannot be diagnosed by CT. Enhanced CT of the pelvis is used for subjects with suspected pelvic metastases. Bone scan is performed only when clinically indicated and must be performed within 42 days prior to the first dose. If clinically indicated, appropriate methods may be used to examine any other known or suspected disease site.

- During the screening period, tumor evaluation could be based on the imaging results obtained within 4 weeks prior to the first dose of the investigational drug and prior to the signature of the informed consent, as long as they met the requirements of RECIST 1.1.
- During the study treatment period, imaging examination will be performed once every 6 weeks (±7 days) in the first 12 months, and then once every 9 weeks (±7 days) thereafter. When a subject withdraws from the study for any reason, imaging examination is required at the treatment discontinuation visit (if the time from the previous examination to the treatment withdrawal is not more than 4 weeks, no re-examination is required at the time of withdrawal). The conditions for imaging examination should be the same as those at baseline (including scanning slice thickness, contrast agent, etc.). Imaging examination is allowed with a window period of ±7 days, and unscheduled imaging examination may be performed when disease progression is suspected (e.g., symptoms deteriorate).
- Subjects without radiographic progression at safety and survival follow-up should still be evaluated by imaging as frequently as possible until Disease progression, initiation of alternative anti-tumor therapy, withdrawal of consent, loss to follow-up, or death.

[15] Tumor tissue samples: subjects should provide tumor tissue samples. Fresh specimen (preferred) or formalin-fixed, paraffin-embedded tumor tissue blocks or unstained tumor specimen sections, at least 8 unstained sections (for subjects with oropharyngeal cancer, if there is no HPV16 test result in the past, 2 more sections are required). At the same time, 2 ml of whole blood should be collected for sequencing paired detection. Except that subjects in Phase II Cohort B must provide qualified tumor tissue samples for PD-L1 detection, subjects who cannot provide qualified tumor tissue samples can also be enrolled after discussion and agreement by the investigator and the sponsor.

[16] Pharmacokinetic blood collection: The time points for blood collection in subjects participating in phase Ib study are as follows: within 0.5 h before administration of the first dose in Cycle 1 and Cycle 3, immediately after the end of administration of JS001 (within 10 min, only JS001 is determined), immediately after the end of administration of cetuximab (within 10 min), 2 h (±5 min) after the end of cetuximab administration, 24 h (±1 h), 48 h (±2 h), 96 h (±2 h), 168 h (±8 h, before the second dose of cetuximab), 336 h (±12 h, before the third dose of cetuximab), 504 h (±24 h, before the next dose), immediately after the end of administration of JS001 in Cycle 2 D1 (within 10 min, only JS001 is determined), immediately after the end of administration of cetuximab in Cycle 2 D1 (within 10 min). The concentrations

of cetuximab and JS001 are determined at each blood collection point. 4 mL of blood is collected at each blood collection point (2 mL is collected at the point for only determination of JS001), and the specific treatment is detailed in the laboratory manual.

[17] Immunogenicity blood collection: 6 mL blood will be collected at each time point (3 mL if single drug is measured). Blood samples will be collected before the first dose, before D1 in Cycle 2 and Cycle 4, once a year within the first year thereafter, once every 24 weeks from the second year onwards (on the day of administration, before administration) for determination of anti-drug antibody (ADA) and Drug trough level of JS001 and cetuximab. The immunogenicity will be evaluated in relation to pharmacokinetics, safety and efficacy until discontinuation of study treatment or end of study (whichever occurs first).

[18] Study drug administration: the administration cycle is 21 days. The specific administration dose is as follows:

| **Dose group** | **Investigational product** | **Every cycle (21 days)** | | |
|---|---|---|---|---|
| | | **Day 1** | **Day 8** | **Day 15** |
| **Initial dose group** | Toripalimab | 240mg | / | / |
| | Cetuximab | 400 mg/m$^2$ in the first cycle<br>250 mg/m$^2$ in subsequent cycles | 250mg/m$^2$ | 250mg/m$^2$ |
| **alternate dose group** | Toripalimab | 240mg | / | / |
| | Cetuximab | 400 mg/m$^2$ in the first cycle<br>200 mg/m$^2$ in subsequent cycles | 200mg/m$^2$ | 200mg/m$^2$ |

[19] Adverse Event: AE/SAE will be collected from the signing of the informed consent form to the end of the safety follow-up period (60 days ± 7 days after the last dose) or the start of a new anti-tumor therapy (whichever comes first). Subsequently, only SAEs related to the study drug JS001 will be recorded. Adverse events should be followed up until they are resolved, stabilized, the event is explained, or the patient is lost to follow-up.

[20] Concomitant medication/therapy: Concomitant medications/therapies were recorded from 28 days prior to the first dose of study medication to the Therapy cessation visit. Concomitant medications/therapies related to AEs were recorded only after the Therapy cessation visit.

[21] Treatment cycle: Each treatment cycle is 21 days. The ± 3 days visit window on D1 is only applicable to cycles 2 and subsequent cycles.

[22] Treatment termination visit: It should be performed ±7 days when the decision for therapy cessation and/or withdrawal from the study is made. If the imaging examination for efficacy evaluation is completed within 4 weeks before treatment withdrawal and the examination for safety evaluation is completed within 7 days, the examination does not need to be repeated at this stage.

[23] Safety follow-up: The safety follow-up will be performed every 30 days (±7 days) from the last study treatment until Day 60 after the last study treatment. Survival information and Adverse Events can be collected through an effective way, such as a telephone interview.

[24] Survival follow-up: After the end of the safety follow-up period, subjects entered survival follow-up until death, loss to follow-up, withdrawal of informed consent, or study termination by the Sponsor. During this period, one visit was made through telephone follow-up and other effective visits every month to collect survival information and subsequent treatment information (if the subject started new anti-tumor treatment, the treatment regimen and start and end dates should be recorded).

[25] Subsequent anti-tumor therapy: the subsequent anti-tumor therapy will be collected until the subject withdraws the informed consent, is lost to follow-up, dies, or the sponsor terminates the study, whichever comes first.

# 2 INTRODUCTION

## 2.1 Study background

### 2.1.1 Current Treatment Status of Recurrent or Metastatic Squamous Cell Carcinoma of Head and Neck

Head and neck cancer refers to tumors occurring in the mouth, nose, pharynx, larynx, etc., more than 90% of which are squamous cell carcinomas and their variants, collectively known as Squamous cell carcinoma of head and neck (HNSCC).

According to the 2018 GLOBOCAN, the number of new cases of head and neck cancers (except Nasopharyngeal cancer) is about 706,000 per year, ranking 8th; the number of deaths is about 358,000, ranking 8th. It accounts for 3.9% of the total number of new cases of Neoplasm malignant and 3.8% of the total number of deaths worldwide in 2018. The data in China showed that it is predicted that the number of new cases and deaths of head and neck cancers (except Nasopharyngeal cancer) in 2015 were 48,100 and 22,100, respectively, accounting for 1.12% and 0.79% of the total number of new and death cases in China, respectively.[1,2]

More than 65% of head and neck squamous cell carcinomas are already metastatic at presentation. After treatment, 15-40% of patients with locally advanced disease will still have recurrence or metastatic, and the 5-year survival rate is less than 50%.[3]

The prognosis of recurrent or metastatic Squamous cell carcinoma of head and neck is poor and the survival time is short. Because its anatomical location is mostly important organs, it will also damage the appearance, basic physiological function, sensory function and language function of patients, thereby affecting the quality of life of patients. Therefore, exploring more effective therapeutic methods and further prolonging the survival of patients with recurrent or metastatic Squamous cell carcinoma of head and neck and improving their quality of life become one of the urgent clinical needs to be solved.

For first-line treatment of head and neck squamous cell carcinoma (except Nasopharyngeal cancer), platinum-based regimens (platinum combined with fluorouracil or taxane ± cetuximab) are currently recommended as the standard treatment in domestic guidelines [4]. For recurrent or

metastatic head and neck squamous cell carcinoma after first-line platinum-based chemotherapy Treatment failure, there is currently no standard treatment. For patients with PD-L1 ≥ 1%, nivolumab can be used. However, for patients without biomarker screening, the current treatment is mainly single-agent chemotherapy such as methotrexate and docetaxel, with a response rate of less than 10% and a median overall survival of 6-7 months.[5,6]

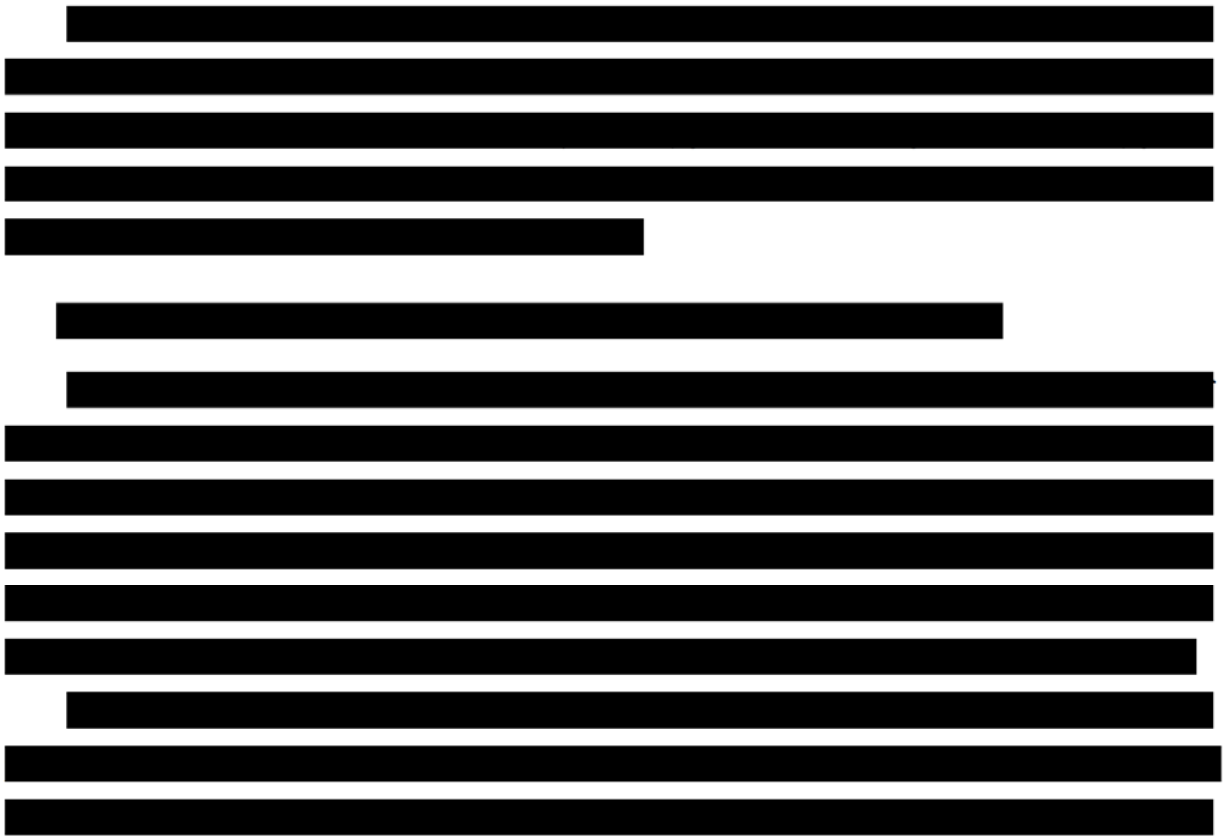
### 2.1.2 Background of Toripalimab (JS001) Drug

The active ingredient of Toripalimab Injection is a novel recombinant humanized (97% degree) anti-PD-1 monoclonal antibody [redacted] which belongs to human IgG4/Kappa subtype, and a serine protein site (Serine to Proline, S228P) at the 228th amino acid site of the IgG4 heavy chain hinge (hinge) region is introduced to increase the stability of the antibody and reduce possible IgG4 Fab chain displacement. Compared with nivolumab and pembrolizumab, another therapeutic monoclonal antibodies targeting the same target, toripalimab has different complementarity determining regions (CDR) and higher affinity, which can specifically bind to PD-1 and effectively block the Interaction between PD-1 and its ligands PD-L1 (i.e., B7-H1) and PD-L2 (i.e., B7-DC), thereby activating cytotoxic Lymphocytes and inhibiting tumor growth. For details of the preclinical and clinical studies of JS001, please refer to the JS001 Investigator's Brochure.

[redacted]

#### 2.1.2.1 Pharmacodynamics

JS001 has high affinity for human PD-1 and does not cause complement-dependent cytotoxicity (CDC), antibody-dependent cytotoxicity (ADCC) and cytokine storm. The in vitro pharmacodynamic study showed that in antigen memory response experiments, JS001 could significantly stimulate antigen-specific T cell proliferation and promote IFN-γ release. The in vivo pharmacodynamic study showed that in the NSG mouse model, after adoptive transfer of human peripheral blood mononuclear cells (PBMC), JS001 could effectively increase the proliferation of human CD4+ and CD8+ T cells in vivo, while promoting the activation of human effector/memory T cells, and its stimulating effect was significantly stronger than that of the same target drug, nivolumab, that has been marketed abroad. JS001 can eliminate the immunosuppression of T cells in the tumor microenvironment and promote the killing effect of cytotoxic T lymphocytes (CTL) on tumor cells. In PD-1 humanized mice, JS001 can significantly inhibit the growth of MC38 colon cancer tumors.



[redacted]

### 2.1.3 Background of cetuximab therapy

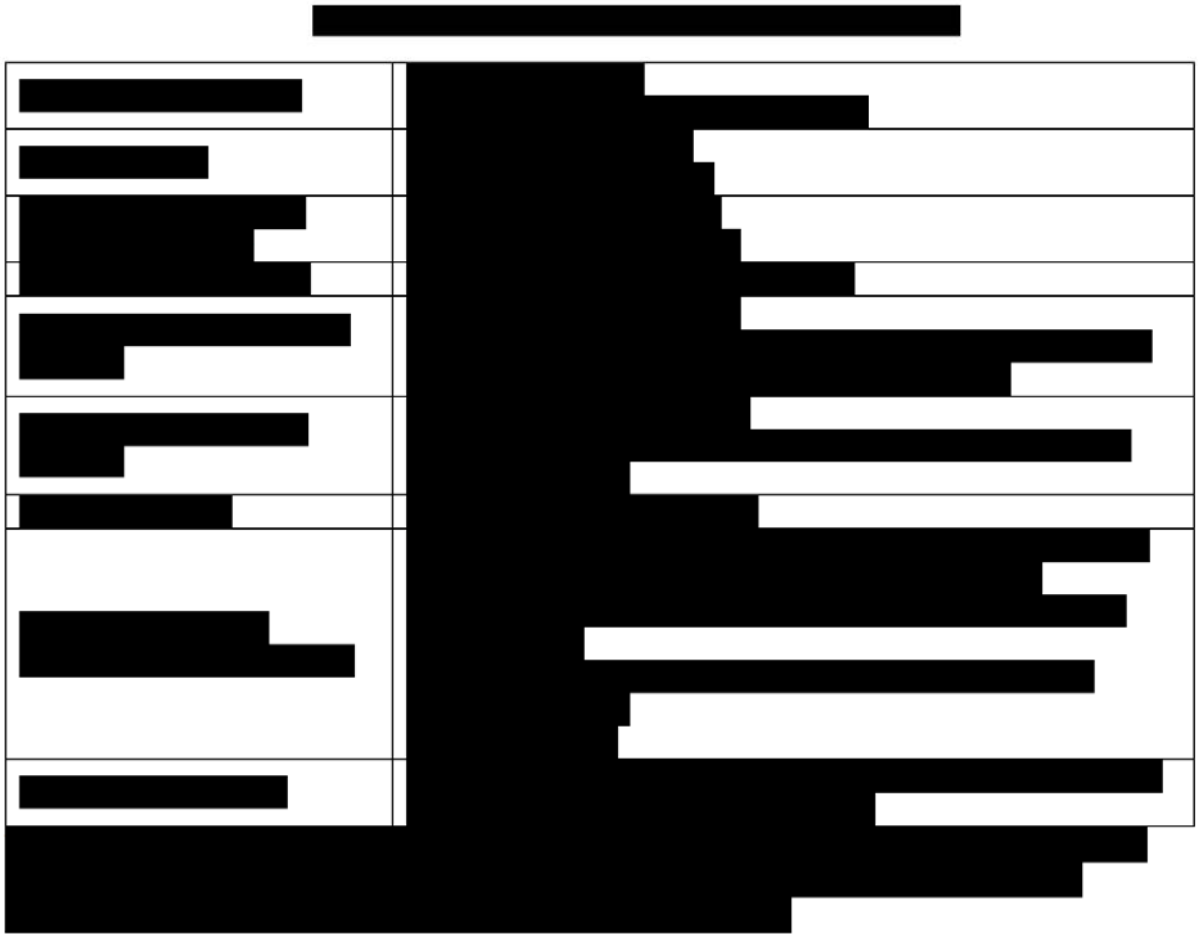
Cetuximab is an antibody against epidermal growth factor receptor (EGFR), which blocks the binding of EGF and other ligands to EGFR, preventing EGFR dimerization, and thus inhibits ligand-induced activation of this receptor tyrosine kinase. This leads to inhibition of cell growth, induction of apoptosis, and reduction of synthesis of matrix metalloproteinases and vascular endothelial growth factor. Cetuximab also prevents Interaction with its ligand by eliminating receptors on the cell surface, stimulating EGFR internalization and ultimate degradation. In addition, cetuximab can mediate antibody-dependent, cell-mediated cytotoxicity, which depends both on the affinity of cetuximab for the extracellular domain of EGFR and on the level of EGFR expression on the cell.

Cetuximab (trade name: Erbitux) has been approved for marketing authorization in many countries around the world for the treatment of colorectal carcinoma and the treatment of squamous cell carcinoma of head and neck (HNSCC). Indications include metastatic colorectal carcinoma (in combination with irinotecan and/or monotherapy) and squamous cell carcinoma of head and neck (HNSCC) (in combination with radiotherapy [locally advanced HNSCC], in combination with platinum-based chemotherapy and/or as monotherapy [for the treatment of recurrent or metastatic disease]).

[redacted]

[redacted]

[redacted]



## 2.2 Scientific basis

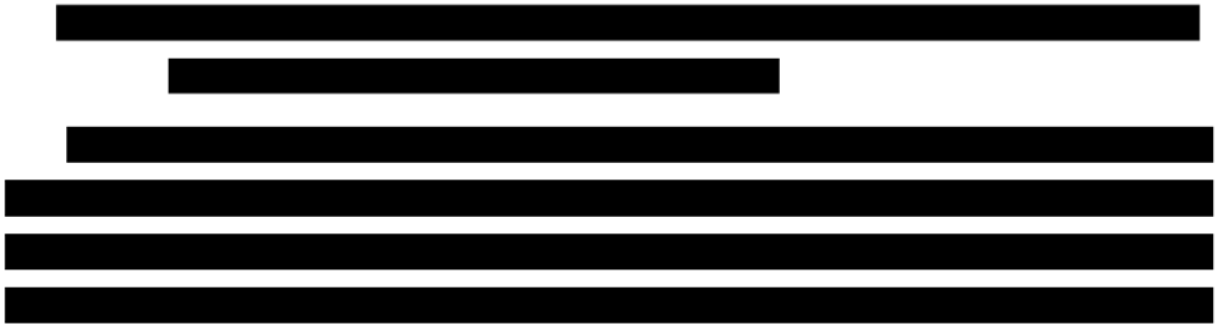
### 2.2.1 Study Progress of PD-1 Inhibitors for Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

#### 2.2.1.1 Progress in the study of similar drugs

Currently, PD-1 inhibitors have shown efficacy in recurrent or metastatic head and neck squamous cell carcinoma. A phase III controlled study KEYNOTE-048 [7] showed that pembrolizumab combined with chemotherapy compared with standard chemotherapy (EXTREME regimen) significantly improved overall survival (14 months vs. 10.7 months, HR 0.77 [0.63, 0.93], p = 0.007). And in the PD-L1 positive population, pembrolizumab monotherapy compared with standard therapy significantly improved overall survival: for CPS≥1 population, the median OS

was 14.9 months vs. 10.7 months, HR 0.61 [0.45-0.83], p < 0.001. For CPS≥20 population, the median OS was 12.3 months vs. 10.3 months, HR 0.78 [0.64-0.96]; p = 0.009. Based on this study, pembrolizumab has been approved overseas for monotherapy in people with PD-L1 CPS≥1 and for combination with platinum and 5-FU in first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma; it has been approved domestically for monotherapy in people with PD-L1 CPS≥20.

There are also similar drugs showing efficacy in patients with recurrent or metastatic head and neck squamous cell carcinoma after treatment failure of platinum-based chemotherapy. A phase III study CheckMate-141 [8] showed that in patients with recurrent or metastatic head and neck squamous cell carcinoma after treatment failure of platinum-based chemotherapy, the overall survival was significantly improved with nivolumab compared with single-agent chemotherapy (8.7 months vs. 4.6 months, HR 0.55 [0.36-0.83]) in the population with PD-L1 ≥ 1%. Based on this study, nivolumab has been approved in China for patients with PD-L1 ≥ 1% after treatment failure of platinum-based chemotherapy. A phase Ib study KEYNOTE-012 [9] showed that in patients with recurrent or metastatic head and neck squamous cell carcinoma after treatment failure of platinum-based chemotherapy, the ORR was 18% and PFS was 2 months with pembrolizumab monotherapy. Based on this study, pembrolizumab has been approved in foreign countries for patients after treatment failure of platinum-based chemotherapy. Another phase III study KEYNOTE-040 [10] showed that in patients with recurrent or metastatic head and neck squamous cell carcinoma after treatment failure of platinum-based chemotherapy, the overall survival was improved with pembrolizumab compared with single-agent chemotherapy (8.4 months vs. 6.9 months, HR 0.80 [0.95-0.98]; p = 0.016).



[redacted]

2.2.2 study of Cetuximab in Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck

Based on a global phase III study EXTREME and a Chinese phase III study CHANGE-2, it has been confirmed that the survival of patients can be significantly prolonged by combining cetuximab with platinum and 5-FU chemotherapy (data are shown in the table below). Cetuximab has been approved for use as first-line treatment in China.

| **Study name** | **Treatment group** | **Number of Patients** | **ORR** | **PFS, month** | **OS, months** |
|---|---|---|---|---|---|
| EXTREME [11] | Cetuximab | 222 | 36% | 5.6(5.0-6.0) | 10.1(8.6-11.2) |

| | | | | | |
|---|---|---|---|---|---|
| | +Platinum-based chemotherapy | | | HR0.54[0.43-0.67]<br>p<0.001 | HR 0.80[0.64-0.99]<br>p=0.04 |
| | Platinum-based chemotherapy | 220 | 20% | 3.3(2.9-4.3) | 7.4(6.4-8.3) |
| CHANGE-2 [12] | Cetuximab plus Platinum-based chemotherapy | 164 | 50% | 5.5(5.4-5.6)<br>HR0.57[0.40-0.80],p=0.001 | 11.1(9.7-12.7)<br>HR 0.69[0.50-0.93] |
| | Platinum-based chemotherapy | 79 | 26.6 % | 4.2(3.0-5.3) | 8.9(6.8-10.9) |

A phase II single-arm study [13] showed that in 103 patients with recurrent or metastatic HNSCC who had experienced treatment failure with prior platinum-based therapy, treatment with cetuximab monotherapy resulted in an ORR of 13% (7%-21%) and a DOR of 5.8 months (1.2-5.8). Based on this study, cetuximab has been approved for use in patients with recurrent or metastatic head and neck squamous cell carcinoma who have experienced treatment failure with platinum-based therapy abroad.

### 2.2.3 Exploration of PD-1 Inhibitor Combined with Cetuximab in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

A multicohort phase II study [14] enrolled 33 patients with recurrent or metastatic head and neck squamous cell carcinoma, 29 of whom had not received systemic therapy for recurrence or metastatic disease previously, and 4 of whom had failed first-line therapy; treatment with cetuximab combined with pembrolizumab resulted in an ORR of 45%, a DCR of 61%, a median follow-up of 7.3 months, a median response duration of 13.1 months, a median stable response time of 8.9 months, and a median OS of 18.4 months. The safety was tolerable: 13 grade 3 treatment-related AEs (TRAEs) and 1 grade 4 TRAE occurred. No treatment-related deaths occurred. The most common ≥3-grade TRAE was stomatitis (3 patients [9%]). Treatment-related

SAEs were colitis (2 patients [6%]), throat edema (1 patient with 2 AE [3%]), acidosis (1 patient [3%]), and septicaemia (1 patient [3%]).

In a phase I study [15], 10 patients with locally advanced head and neck squamous cell carcinoma were treated with cetuximab combined with Avelumab and concurrent radiochemotherapy. After a median follow-up of 12 months, 4 subjects had no recurrence. Safety: 4 subjects had grade 3 drug-related Adverse Events (1 with Rash maculo-papular and 3 with Hepatic enzyme increased); no grade 4 or 5 Adverse Events were reported.

A retrospective study in Taiwan [16] found that in 15 patients with recurrent or metastatic head and neck squamous cell carcinoma, combination therapy with cetuximab, a PD-1 inhibitor, and low-dose chemotherapy had an ORR of 66.7% and was tolerable.

In a phase II study [17] exploring the combination of cetuximab and nivolumab in patients with recurrent or metastatic HNSCC who had experienced treatment failure, a total of 45 patients were analyzed, with a median PFS of 3.4 months, 1-year PFS rate of 19%, median OS of 11.5 months, and 1-year OS rate of 44%; of which 22 patients (49%) had not received prior immune checkpoint inhibitor therapy, with a median PFS of 6.0 months, 1-year PFS rate of 32%, and median OS of 13.3 months, 1-year OS rate of 60%. The most common grade 3 TRAEs were fatigue in 6 patients (13%) and rash-acne in 2 patients (4.4%). The only grade 4 TRAE was infusion reaction of cetuximab in 1 patient (2.2%). The most common grade 3 immune-related AE (irAE) was fatigue in 3 patients (6.7%). No grade 4 irAE was observed.

An exploratory study of cetuximab combined with nivolumab in previously untreated patients with recurrent or metastatic HNSCC [18] enrolled 54 patients, with a median PFS of 7.8 months and a median OS of 14.5 months; the 1-year PFS and OS rates were 39% and 61%, respectively. The most common TRAEs were hypomagnesaemia in 2 patients (4%), hypophosphataemia in 2 patients (4%), fatigue in 4 patients (7%), and rash-acne in 4 patients (7%). The only grade 4 TRAE was hypomagnesaemia in 1 patient (2%) and cetuximab infusion reaction in 1 patient (2%). The most common grade 3 irAE was fatigue in 2 patients (4%). No grade 4 irAE was observed.

The above small sample studies all suggested that the combination of cetuximab and PD-1 inhibitors showed preliminary efficacy and was tolerable, and was worth exploring.

## 2.3 **Benefit/Risk Assessment**

### 2.3.1 Risk Assessment

The majority of adverse drug reactions observed with immune checkpoint inhibitors are due to the effect of inflammatory cells on specific tissues. These risks are usually referred to as having potential inflammation or immune-mediated events, which may require more frequent monitoring and/or unique interventions, such as immunosuppression and/or endocrine therapy. The immune-mediated effects can occur in almost any organ system. Important risks identified with toripalimab treatment include immune-related pneumonitis, immune-related hepatitis, immune-related colitis and diarrhea, immune-related hyperthyroidism and hypothyroidism, immune-related thyroiditis, immune-related hyperglycaemia and diabetes mellitus, immune-related adrenal cortex insufficiency and hypophysitis, immune-related pancreatitis, immune-related myocarditis, immune-related myositis, immune-related nephritis, immune-related skin toxicity, and infusion related reaction. Important potential risks of toripalimab treatment include, but are not limited to, immune-related ocular toxicity and neurotoxicity, reproductive embryotoxicity, etc. Most immune-mediated adverse events can be adequately controlled under the established toxicity management procedures. For safety data on toripalimab treatment, including a detailed summary of treatment-related AEs, SAEs, and CTCAE Grade 3 and above events reported in each study, see the current version of the IB.

The common adverse reactions of cetuximab mainly include skin reaction, diarrhea, infusion reaction, and hypomagnesaemia. The theoretical toxicological synergies of toripalimab combined with cetuximab are interstitial pneumonia and keratitis. Risk management will be conducted through strict inclusion and exclusion criteria, close medical monitoring, and the company's routine pharmacovigilance to ensure patient safety.

### 2.3.2 Benefit Assessment

Head and neck squamous cell carcinoma is a common type of neoplasm malignant that seriously threatens the survival and quality of life of patients. There is currently no standard treatment for recurrent or metastatic head and neck squamous cell carcinoma that has experienced treatment failure with first-line platinum-based chemotherapy. For patients with PD-L1 ≥ 1%, nivolumab can be used. However, for patients without biomarker screening, the current treatment is mainly single-agent chemotherapy such as methotrexate and docetaxel, and the response rate is less than 10%, the overall survival is 6-7 months, and there is an unmet clinical need. For HNSCC patients who have not received systemic treatment for recurrent or metastatic disease, cetuximab combined with chemotherapy, as well as pembrolizumab monotherapy in the PD-L1 selected population are the current standard treatments. However, the safety of the combination chemotherapy regimen needs to be improved, and the response rate and progression-free survival of pembrolizumab monotherapy need to be improved, and there is an unmet clinical need.

Both cetuximab and PD-1 inhibitors have been proven effective in head and neck squamous cell carcinoma, and their combined use is promising. Previous data on toripalimab showed a similar efficacy and good tolerability in recurrent or metastatic head and neck squamous cell carcinoma as its counterparts. There have been small-sample studies of cetuximab combined with PD-1 inhibitors in recurrent or metastatic head and neck squamous cell carcinoma that have shown efficacy, so cetuximab combined with toripalimab may improve survival in patients with recurrent or metastatic head and neck squamous cell carcinoma.

### 2.3.3 Overall Benefit/Risk Conclusion

Preclinical, clinical pharmacology, and current clinical data show that toripalimab and cetuximab are effective and well tolerated in head and neck squamous cell carcinoma. The combination has a positive benefit/risk ratio and is worth exploring in patients with recurrent or metastatic head and neck squamous cell carcinoma.

The toxicity of toripalimab monotherapy and in combination with cetuximab is generally manageable through the design of this study and toxicity management guidelines for immune-related Adverse Events and infusion-related reactions. The benefit-risk profile of toripalimab remains favorable and supports the clinical development of this indication.

# 3 STUDY OBJECTIVES AND ENDPOINTS

## Study Objectives

| | Phase Ib study | Phase II study |
|---|---|---|
| **Primary Objectives** | ・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. | ・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 tumour version 1.1 (RECIST 1.1). |
| **Secondary Objectives** | ・To determine the recommended phase II dose (RP2D) of the combination regimen in patients with recurrent or metastatic HNSCC.<br>・To evaluate the pharmacokinetic (PK) profile of the combination regimen in patients with recurrent or metastatic HNSCC.<br>・To evaluate the efficacy of the combination regimen in the treatment of recurrent or metastatic HNSCC. | ・To evaluate the efficacy of the combination regimen in terms of disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS) in patients with recurrent or metastatic HNSCC.<br>・To evaluate the efficacy of the combination regimen in patients with recurrent or metastatic HNSCC using overall survival (OS) and 1-year OS rate.<br>・To further evaluate the safety and tolerability of the combination regimen in patients with recurrent or metastatic HNSCC. |
| **Exploratory study objectives** | ・To evaluate the efficacy of the combination regimen in patients with recurrent or metastatic HNSCC using Immune-related Response Evaluation Criteria in Solid tumour (iRECIST).<br>・Test biomarkers and evaluate their relationship with efficacy.<br>・To evaluate the immunogenicity of JS001 and cetuximab. | |

**Study Endpoints**

| | Phase Ib study | Phase II study |
|---|---|---|
| **Primary Endpoints** | · 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. | · Cohort A: ORR assessed by IRC according to RECIST v1.1.<br>· Cohort B: ORR assessed by investigators according to RECIST 1.1. |
| **Secondary Endpoints** | · Recommended Phase II dose (RP2D) for the combination regimen.<br>· PK parameters of toripalimab and cetuximab: clearance (CL), volume of distribution (Vss), AUC, Cmax, Ctrough and t1/2.<br>· ORR, DCR, DOR, PFS evaluated by the IRC and the investigator according to RECIST 1.1<br>· OS and 1-year OS rate. | · Cohort A: ORR assessed by investigators according to RECIST 1.1.<br>· Cohort A: DCR, DOR and PFS assessed by IRC and by the investigator according to RECIST 1.1.<br>· Cohort B: DCR, DOR and PFS assessed by the investigator according to RECIST 1.1<br>· OS and 1-year OS rate.<br>· 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. |
| **Exploratory Endpoint** | · iORR, iDCR, iDOR, and iPFS evaluated according to iRECIST.<br>· Correlation between PD-L1 expression, HPV status (only applicable to oropharyngeal cancer), tumor mutation burden and efficacy.<br>· Positive anti-tumor antibody response to JS001 and anti-cetuximab antibody will be correlated with PK parameters, safety and efficacy data. | |

# 4 STUDY DESIGN

## 4.1 Overall Design

This is an open-label, multi-center Phase Ib/II clinical study. The Phase Ib study phase is mainly 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 mainly 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 mainly used to evaluate the efficacy and safety of the combination regimen in the treatment of PD-L1-positive HNSCC without previous systemic therapy for metastatic disease.

The study includes a screening period, a treatment period and a follow-up period. The screening period is no longer than 28 days. After completion of the screening period examinations and assessments, eligible patients will enter the study treatment period. Patients should receive study treatment as specified in the protocol until disease progression by radiological criteria according to RECIST 1.1, intolerable toxicity, patient request to discontinue study treatment or withdraw informed consent, or investigator's judgment that treatment withdrawal is necessary, or up to 2 years of treatment (whichever occurs first).

Safety data were collected continuously during the study. The incidence and severity of Adverse Events were assessed for safety and tolerability according to the NCI-CTCAE v5.0 criteria. Laboratory tests, vital signs, ECOG performance status, Physical examination, ECG, and Adverse Events were assessed continuously during the trial.

Tumor evaluation was performed at screening (as baseline), every 6 weeks (±7 days) within the first 12 months, and every 9 weeks (±7 days) thereafter until radiographic documentation of disease progression (PD), iCPD judged by the investigator (for subjects with the first radiographic presentation of PD but judged by the investigator to be able to continue treatment), withdrawal of informed consent, loss to follow-up, initiation of new anti-tumor therapy, or termination of the study. Subjects who drop out of the study for reasons other than non-disease progression (including drop out due to AEs or treatment interval out of window), and do not experience disease progression at the time of drop out, will continue to undergo radiographic evaluation until disease progression, death, loss to follow-up, or initiation of new anti-tumor therapy. The management of the subject's treatment will be based on the tumor evaluation results of the investigator.

For patients who present with disease progression on imaging according to RECIST1.1, the treatment can be continued as long as the investigator judges that the patient can still benefit from the drug treatment and after discussion with the medical monitor of the sponsor. The clinical

benefit is evaluated by the investigator based on the iRECIST, taking into account the imaging findings and clinical condition, in the absence of intolerable toxicity or worsening of symptoms due to disease progression.

All subjects should have immunogenicity blood samples and pharmacokinetic blood samples collected according to the protocol for corresponding immunogenicity and pharmacokinetic analysis. In addition to the subjects in Phase II Cohort B who must provide a qualified tumor tissue sample for PD-L1 testing, all subjects must also provide a qualified tumor tissue sample. Subjects who are unable to provide a qualified tumor tissue sample may also be enrolled after discussion and agreement between the investigator and the sponsor.

## 4.2 Phase Ib study

### 4.2.1 Study Design

A cycle consists of 21 days. Toripalimab will be administered on Day 1 of each cycle, followed by observation for approximately 60 minutes, and then cetuximab will be administered. The specific dosing regimen is provided in the table below:

| Dose group | Investigational product | Every cycle (21 days) | | |
|---|---|---|---|---|
| | | Day 1 | Day 8 | Day 15 |
| Initial dose group | Toripalimab | 240mg | / | / |
| | Cetuximab | 400 mg/m$^2$ in the first cycle<br>250 mg/m$^2$ in subsequent cycles | 250mg/m$^2$ | 250mg/m$^2$ |
| alternate dose group | Toripalimab | 240mg | / | / |
| | Cetuximab | 400 mg/m$^2$ in the first cycle<br>200 mg/m$^2$ in subsequent cycles | 200mg/m$^2$ | 200mg/m$^2$ |

First, 6 patients were enrolled to receive the initial dose as the tolerability observation period of the first dosing cycle (21 days). If <2 patients developed dose-limiting toxicity (DLT), then 6 patients were enrolled (total 12 patients) to collect adequate safety and PK data of the combination

therapy. The SMC determined whether the dose could be used as the recommended dose for phase II based on the safety and PK data of 12 patients.

If DLT occurs in ≥2 patients in the first 6 patients, the dose will be adjusted to the alternative dose and enrollment and observation will be performed according to the above enrollment plan. If DLT occurs in ≥2 patients in the first 6 patients in the alternative dose group, SMC will decide whether to use other dose levels/dose cycles for the study based on the available safety and PK data.

If a patient is discontinued from the study due to a non-drug-related Adverse Event or an Adverse Event that does not meet the criteria for dose interruption/reduction, and the actual dose of toripalimab or cetuximab in the first cycle is less than 80% of the expected dose, the patient will be replaced after discussion and agreement by SMC.

#### 4.2.2 Dose-limiting toxicity criteria

The severity of Adverse Events will be graded according to NCI-CTCAE version 5.0.

During the Ib phase, any of the following toxicities that occurred during the tolerability observation period (within 21 days after the first dose) and were related to the study drug would be considered as dose-limiting toxicity:

1. Grade ≥3 hematologic toxicity, defined as follows:

   1) Grade 4 Neutropenia, lasting ≥5 days;

   2) Grade ≥3 febrile neutropenia;

   3) Grade 3 platelet count decreased, lasting for ≥ 7 days, or with obvious hemorrhagic manifestations;

   4) Grade 4 platelet count decreased, for ≥ 5 days;

   5) Grade ≥4 anemia.

2. Grade ≥3 non-hematologic toxicity, except:

1) Nausea, vomiting, diarrhea, and weakness of ≥ Grade 3 were improved to ≤ Grade 2 within 3 days with symptomatic supportive treatment;

2) Grade 3 Infusion reaction or Grade 3 fever (symptomatic supportive treatment may be used), lasting no more than 6 hours;

3) Grade 3 skin toxicity improved to ≤ grade 2 within 7 days of symptomatic supportive treatment;

4) Asymptomatic ≥ Grade 3 laboratory test abnormalities improve to ≤ Grade 2 or baseline within 3 days of symptomatic supportive treatment;

5) Isolated grade 3 or greater amylase or lipase investigation abnormal.

3. Dose of cetuximab <80% of the projected dose due to relevant toxicity.

4. Other unexpected, persistent toxicity that, in the judgment of the SMC, requires discontinuation of the studied treatment.

4.2.3 Safety Monitoring Committee

An external Safety Monitoring Committee (SMC) will be established for this study, including investigators and the Sponsor's safety review team. For the study objectives of this protocol, the Sponsor will conduct regular safety reviews through an internal safety review team with medical and statistical capabilities. The review will include individual and summary data on safety and the clinical database. Review measures include:

Monitors serious Adverse Events in accordance with regulatory guidance.

The investigator and the sponsor will discuss the Adverse Events and Laboratory test abnormalities at each dose level through regular remote meetings and/or meetings to determine safety data and risk/benefit ratio, and to confirm whether it is appropriate to continue enrollment. After completion of the safety evaluation in the initial dose group, the investigator and the sponsor will discuss the safety data obtained through meetings (including telephone or video conference) and/or email, as appropriate, and determine whether to use the alternative dose, as well as confirm the final RP2D.

### 4.3 Phase II study

The patients participating in the phase II study will receive toripalimab in combination with cetuximab at the RP2D established in the phase Ib study. Until disease progression on imaging as judged by the investigator according to RECIST 1.1, intolerable toxicity, patient's request to discontinue study treatment or withdraw informed consent, investigator's judgment that treatment withdrawal is needed, or up to 2 years of treatment (whichever comes first). The phase II study consists of two cohorts, cohort A planned to enroll 45 patients (including patients at the same dose in the phase Ib study) and cohort B planned to enroll 43 patients.

### 4.4 End of Study

The end of study is defined as 18 months after the enrollment of the last subject.

## 5 STUDY POPULATION

### 5.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be enrolled in this study:

1. Patients who are willing to participate in this study and sign the informed consent form on a voluntary basis after adequate informed consent;
2. Aged ≥18 and ≤75 at time of signing ICF;
3. Histologically or cytologically confirmed advanced, recurrent, or metastatic head and neck squamous cell carcinoma originating in the oral cavity, oropharynx, hypopharynx, larynx, or paranasal sinuses, not amenable to local treatments such as surgery or radiotherapy;
4. Ib cohort A: patients who have received first-line platinum-based chemotherapy for recurrent and metastatic disease and developed progressive disease during or after treatment, or have received a platinum-based regimen as neoadjuvant or adjuvant chemotherapy (or Radiochemotherapy) and developed recurrence or metastatic disease within 6 months after treatment completion.
5. Phase II Cohort B:

   1) No previous systemic therapy for recurrent or metastatic disease. If previous systemic therapy was used as part of local therapy, recurrence or metastasis occurred more than 6

months after the end of treatment.

2) Patients must provide a qualified tumor tissue sample and PD-L1 expression is positive as determined by central Lab test (positive definition as Combined Positive Score (CPS) ≥ 1).

6. All acute toxicities resulting from prior anticancer therapy, surgery, or radiotherapy must have resolved to Grade 0-1 (per NCI-CTCAE v5.0) or to the level specified in the inclusion/exclusion criteria. Exceptions include alopecia, pigmentation, or other toxicities deemed by the investigator to pose no safety risk to the subject and not affecting treatment compliance.
7. An archival tumor specimen or fresh tumor biopsy sample is available.
8. For subjects with Oropharyngeal cancer, a report of prior HPV16 test or qualified tumor tissue samples for HPV status test can be provided.
9. At least one measurable lesion according to RECIST 1.1;
10. Expected survival ≥12 weeks;
11. Eastern Cooperative Collaboration Oncology Group (ECOG) performance status score of 0 or 1;
12. Adequate organ function:

| System Organ | Lab values |
|---|---|
| **Hematology (no history of transfusion or colony-stimulating factor or other drugs used for correction within 14 days prior to the first dose of study drug)** | |
| Neutrophil count | ≥$1.5\times10^9$/L |
| Platelet count | ≥$100\times10^9$/ L |
| Haemoglobin | ≥90 g/L |
| **Renal Function** | |
| Serum creatinine or | ≤ 1.5 × upper limit of normal (ULN) |
| Creatinine clearance calculated using the Cockcroft-Gault formula or center practice | ≥50 mL/min |
| **Liver function** | |
| Bilirubin total | ≤ 1.5 × ULN or<br>≤ 3 ULN (patients with known Gilbert's disease) |
| ALT/AST | ≤ 3 ULN (no metastases to liver)<br>≤5 ULN in presence of metastases to liver |
| Albumin (no infusion of albumin preparations within 14 days prior to the first dose of the study drug) | ≥30 g/L |
| **Coagulation function** | |
| International normalized ratio (INR) | ≤ 1.5 × ULN |

| | |
|---|---|
| Prothrombin time (PT)<br>Activated partial thromboplastin time (aPTT) | |

13. Females of childbearing potential must confirm a negative serum pregnancy test within 72 hours prior to the first dose and agree to use effective contraception during study drug use and for 5 months after the last dose. In this protocol, a female of childbearing potential is defined as:

1) Have not undergone amputation of uterus or bilateral oophorectomy,

2）Natural menopause for no consecutive 24 months (cessation of menstruation after cancer treatment does not exclude fertility) (i.e., having menstruated at any time in the previous consecutive 24 months).

Male patients with sexual partners of childbearing age must agree to use effective contraception during the use of the study drug and for 5 months after the last dose.

### 5.2 Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Histologically or cytologically confirmed nasopharyngeal cancer, salivary gland carcinoma or other non-squamous cell carcinoma (e.g., adenocarcinoma, sarcoma or mixed carcinoma), and metastatic squamous cell carcinoma of unknown primary site;
2. Presence of necrotic lesions with risk of Major bleed as assessed by the investigator.
3. Previous treatment with other immune checkpoint inhibitors/agents targeting the immune checkpoint pathway/other agents that target T cell co-stimulation (e.g., PD-1/PD-L1 antibody or CTLA-4 antibody);
4. Previously treated with EGFR inhibitors (including radiotherapy sensitizers).
5. Diagnosis of other neoplasm malignant within 5 years prior to entry, except for skin basal cell carcinoma or squamous cell carcinoma that has been cured by local treatment, superficial bladder cancer, carcinoma cervix in situ, or carcinoma in situ of breast ductal.
6. Uncontrollable or symptomatic active central nervous system (CNS) metastasis, which may present as clinical symptoms, brain oedema, spinal cord compression, carcinomatous meningitis, leptomeningeal disease and/or progressive growth;

1) Imaging findings indicating asymptomatic spinal cord compression that has been assessed by a specialist as stable and does not currently require intervention are excluded;

2) Excluded are patients who have received treatment for CNS metastases and have demonstrated radiographic stability for ≥4 weeks during the screening period, and have discontinued systemic corticosteroid therapy at a dose >10 mg/day of prednisone or equivalent for ≥4 weeks prior to the first study dose;

7. Poorly controlled Pleural effusion, peritoneal, or Pericardial effusion;

8. Having Grade ≥2 Neuropathy peripheral (per NCI-CTCAE 5.0) or hearing loss;

9. Female patients who are pregnant or breastfeeding;

10. Occurrence of any of the following within 6 months prior to the first study dose: myocardial infarction, severe/unstable angina, cardiac dysfunction of NYHA Class II or higher, clinically significant supraventricular or ventricular arrhythmias, and symptomatic congestive heart failure;

Note: Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on an optimized and stable medical regimen as determined by the treating physician, in consultation with a cardiologist if appropriate;

11. Poorly controlled Hypertension (Blood pressure systolic ≥160 mmHg and/or Blood pressure diastolic ≥100 mmHg) (based on the average of ≥3 BP readings obtained from ≥2 measurements); Hypertensive crisis or hypertensive encephalopathy within 6 months of the first dose;

12. Known allergy to the investigational drug or any of its excipients, or a history of serious allergic reaction to other monoclonal antibodies;

13. Prior use of the following medications or drug therapy prior to the first dose of study drug:

    1) Major surgery within 28 days prior to the first dose of study treatment (tissue biopsy performed for diagnostic purposes and central venous catheterization (PICC) or infusion port implantation through peripheral venous puncture are allowed).

    2) Have received any anti-tumor therapy (including chemotherapy, radiotherapy, immunotherapy, endocrine therapy, targeted therapy, cytokine therapy or biological therapy) within 28 days prior to the first study medication;

    3) Participated in other intervention studies within 28 weeks prior to the first dose of study drug;

4) Received systemic immunomodulatory agents (including but not limited to interferon or IL-2) within 14 days prior to the first study dose or 5 half-lives of the drug, whichever is longer;

5) Have received systemic corticosteroids (>10 mg/day prednisone or equivalent) or other systemic immunosuppressive agents (including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumour necrosis [anti-TNF] drugs) within 14 days prior to the first study dose;

   - Topical, ophthalmic, intra-articular, intranasal, and inhaled corticosteroids were allowed;

   - Patients receiving acute low-dose systemic immunosuppressive agents (such as treatment of nausea with a single dose of dexamethasone, or premedication for cetuximab) can discuss with the medical monitor and obtain approval to be enrolled in the study;

   - Patients who have had previous allergic reactions to intravenous contrast for MRI/CT tumor evaluation at baseline and subsequent tumor assessments may receive preventive use of steroid;

   - Inhaled corticosteroids are allowed for treatment of chronic obstructive pulmonary disease, hydrocortisone (e.g., fludrocortisone) for treatment of patients with Orthostatic hypotension, and low-dose corticosteroids for maintenance treatment of adrenal cortex insufficiency;

6) Received oral or intravenous antibiotic therapy within 14 days prior to the first dose of study drug (except for prophylactic antibiotic therapy);

7) Vaccination with any live vaccine (e.g., vaccine against infectious diseases, such as influenza vaccine, varicella vaccine, etc.) within 28 days prior to the first study dose;

14. History of autoimmune disease, including but not limited to Myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sicca syndrome, Guillain-Barre syndrome, multiple sclerosis, vasculitis or glomerulonephritis;

    1) Patients with thyroid function decreased who are receiving stable doses of thyroid hormone replacement therapy are eligible to participate in this study;

    2) Patients with type I Diabetes mellitus under stable Insulin regimen who have controlled disease are eligible to participate in this study;

15. History of allogeneic organ transplant or allogeneic hematopoietic stem cell transplant;

16. Any serious infection (NCI-CTCAE > grade 2) within 28 days prior to the first dose of study drug, e.g., severe pneumonia, bacteraemia, and infections with complications requiring hospitalisation.

17. Active infection, including but not limited to tuberculosis (clinical diagnosis includes clinical history, physical examination and radiological findings, as well as TB examination according to local medical routine), hepatitis B, hepatitis C or human immunodeficiency virus (HIV antibody positive);

    1) Patients who are positive for hepatitis B surface antigen (HBsAg+) and/or hepatitis B core antibody positive (HBcAb+) need to undergo hepatitis B virus deoxyribonucleic acid (HBV DNA) test. If the HBV DNA copy number is <1000/mL, or <200IU/mL, or <lower limit of detection of the study center, they can participate in this study;

    2) Patients with Hepatitis C antibody positive (HCV Ab+) need to undergo HCV RNA test, and only those with negative HCV RNA (defined as below the lower limit of detection at the study center) are eligible for this study;

18. Idiopathic pulmonary fibrosis, drug-induced pneumonia, organising pneumonia (i.e., obliterative bronchiolitis), radiation pneumonitis with clinical symptoms or requiring steroid treatment, active pneumonia, or other moderate to severe lung disorders significantly affecting lung function.

19. Patients with other serious physical or mental diseases or laboratory test abnormalities, or those with alcoholism or Drug of Abuse, which may increase the risk of participation in the study, affect treatment compliance, or interfere with the study results, as well as patients who, in the judgment of the investigator, are not suitable for participation in this study.

### 5.3 Screen Failure

Re-screening is allowed in this study, i.e., subjects who sign the informed consent form and enter the screening process but do not meet the inclusion and exclusion criteria and have not started study treatment can be re-screened. The test results obtained during the first screening can be replaced by the repeated screening tests if they are within the window period and meet the inclusion and exclusion criteria. A new subject number will be assigned for re-screening. Each subject has only one chance of re-screening.

# 6 STUDY TREATMENTS

## 6.1 Study Drug Information

| Drug Name | Toripalimab Injection (JS001) | Sunitinib Injection (Erbitux) |
|---|---|---|
| Source | Suzhou Zhonghe Biomedical Technology Co., Ltd. | Merck KgaA |
| Dosage form | Intravenous Preparation | Intravenous Preparation |
| Specification | 240 mg/6 mL/vial | 100 mg/20 ml/vial |
| Components | The main active ingredient is Toripalimab. 240 mg toripalimab per vial, 40mg/mL per vial. Excipients: Citric acid monohydrate (3.06 mg), sodium citrate dihydrate (31.80 mg), sodium chloride (17.52 mg), mannitol (150.00 mg), and polysorbate 80 (1.20 mg) | Each 20 mL solution of this product contains: the active ingredient, cetuximab 100 mg; and other ingredients, sodium chloride 116.88 mg, glycine 150.14 mg, polysorbate 80 2 mg, citric acid monohydrate 42.02 mg, pH adjusted with sodium peroxide (1M) to 5.5, and water for injection added to 20 mL. |
| Route of administration | Intravenous infusion | Intravenous infusion |
| Preservation | Stored under refrigeration of 2 °C to 8 °C, protected from light. | Stored under refrigeration of 2 °C to 8 °C, protected from light. |

## 6.2 Method of Use of Investigational Drug

### 6.2.1 Instructions for Use of Toripalimab

Eligible patients will receive 240 mg of JS001 IV infusion once every 3 weeks in a monitored environment, which is equipped with dedicated personnel and adequate emergency equipment/drugs to manage any possible Adverse Events at any time. 240 mg of JS001 is administered intravenously (IV) in a 100 mL 0.9% NaCl infusion bag. The first infusion lasts at least 60 minutes, followed by a 60 (± 10) minute observation period. The vital signs (heart rate, pulse, respiratory frequency, blood pressure and body temperature) of the patient will be recorded

before, during and 60 (± 10) minutes after the infusion. If the first infusion is tolerated and no infusion-related Adverse Reactions of clinical significance occur, the second infusion is allowed for at least 30 minutes and the vital signs (heart rate/pulse, respiratory frequency, blood pressure and body temperature) of the patient will be recorded before and during the infusion. If the first two infusions are tolerated and no infusion-related Adverse Reactions of clinical significance occur, subsequent doses are allowed for at least 30 minutes and the vital signs (heart rate/pulse, respiratory frequency, blood pressure and body temperature) of the patient will be recorded before the infusion.

Some infusion reactions may occur during the subsequent administration period. If infusion-related adverse reactions occur or clinical indications arise during subsequent infusions, vital signs (heart rate/pulse, respiratory frequency, blood pressure, and body temperature) should also be recorded 60 (± 10) minutes after infusion until multiple observations are obtained, and the vital signs are considered stable by the investigator, and the infusion can be stopped and the vital signs are observed. For patients with severe infusion reactions, especially those with severe dyspnoea, bronchospasm, and hypoxaemia, the infusion should be stopped immediately, and the infusion should be resumed after all symptoms disappear and laboratory tests return to normal at the discretion of the investigator. Toripalimab injection (JS001) will be given first on Day 1 of each cycle, and the administration of toripalimab injection (JS001) will be in accordance with the instructions in Table 3.

**Table 3 Dose and Administration of Toripalimab Injection (JS001)3**

| First infusion | Subsequent Infusions |
|---|---|
| • Prior medications are not allowed.<br>• JS001 will be infused over at least 60 minutes.<br>• Vital signs (heart rate/pulse, respiratory rate, blood pressure, and body temperature) will be recorded pre-infusion, during infusion, and 60 (± 10) minutes post-infusion.<br>• If clinically significant infusion-related adverse reactions occur, the infusion rate may be slowed down or interrupted and necessary treatment may be given until the patient's symptoms improve. For patients with serious infusion reactions, especially those with severe dyspnea, bronchospasm and hypoxemia, the infusion should be immediately stopped and the infusion may be resumed at the discretion of the investigator after all symptoms disappear and laboratory tests return to normal.<br>• Inform the patient that delayed symptoms may occur after injection and contact the study doctor if such symptoms occur. | • If the patient experiences clinically significant infusion-related adverse reactions during previous infusions, appropriate pre-treatment measures may be taken during subsequent infusions under the guidance of the investigator.<br>• If the first infusion is tolerated and no infusion-related adverse reactions of clinical significance occur, the second infusion is allowed to be administered over a period of at least 30 minutes, and the patient's vital signs (heart rate/pulse, respiratory rate, blood pressure, and body temperature) must be recorded before, during, and 60 (± 10) minutes after the infusion. If the first two infusions are tolerated and no infusion-related adverse reactions of clinical significance occur, subsequent doses are allowed to be administered over a period of at least 30 minutes.<br>• Some infusion reactions may occur during the subsequent administration period. If infusion-related adverse reactions occur or clinical indications appear in subsequent infusions, vital signs (heart rate/pulse, respiratory rate, blood pressure, and body temperature) should be recorded 60 (± 10) minutes after infusion until multiple observations are made, and the infusion can be stopped after the vital signs are stable as evaluated by the investigator.<br>• For patients with serious infusion reactions, see the treatment for the first infusion. |

Adverse Events related to study drug Overdose should be recorded in accordance with Section 8.13.2.4.7.

### 6.2.2 Use of Cetuximab

| | Dose* | Rate of infusion | Tube flushing with saline (0.9%) at the end of infusion | Prophylactic treatment with appropriate antihistamines |
|---|---|---|---|---|
| First infusion | 400mg/m$^2$ | Up to 5mg/min | Yes | Compulsory |
| Subsequent Infusions | 250mg/m$^2$ | Up to 10mg/min | Yes | recommendations |

*Note: listed as the initial dose group, RP2D will be determined based on the results of the Phase Ib study.

The dose of cetuximab will be determined according to the patient's BSA and must be recalculated prior to each infusion of cetuximab and adjusted accordingly. BSA will be calculated using the Mosteller formula: BSA ($m^2$) = sqrt([height (cm) x weight (kg)] / 3600). The above calculation will be performed based on weight measured at each relevant visit and height measured and recorded at the screening visit.

The maximum infusion rate at the first infusion should not exceed 5 mg/min and that at subsequent infusions should not exceed 10 mg/min. If possible, the infusion of cetuximab should be performed on the same day of each week and the interval between infusions should not exceed 3 days.

Proper pretreatment (e.g., antihistamines, etc., ≥1 h before use of cetuximab) must be given before the first cetuximab infusion. It is recommended that this pretreatment be given before all subsequent cetuximab infusions every 7 days. The vital signs of the subjects must be continuously monitored before, during, and 1 hour after each cetuximab infusion to detect any AEs (e.g., hypersensitivity). During each cetuximab administration, i.e., until the infusion is completed and within 1 hour after the infusion is completed, there should be a physician present. The exact dose, date of infusion, start time and end time of each cetuximab infusion must be accurately recorded.

Erbitux must not be mixed with any other substance and therefore must be administered by a separate infusion pathway. If another intravenous infusion (e.g., hydration) is required while Erbitux is being infused, a second infusion pathway must be used.

#### 6.2.3 Dosing sequence and duration

JS001 is administered first, followed by the infusion of cetuximab after about 60±10min of observation.

All patients should receive treatment with cetuximab and JS001 until radiographic disease progression according to RECIST 1.1, intolerable toxicity, patient request to discontinue study treatment or withdraw informed consent, or investigator's judgment that treatment withdrawal should occur, or until a maximum of 2 years of treatment has been reached (whichever occurs first). If treatment with one of the drugs is delayed or discontinued, treatment with the other drug should continue.

## 6.3 Dose Modification of Investigational Product

### 6.3.1 Dose Modification of Toripalimab

Dose adjustment of the study drug is not allowed in this study. If a patient experiences an Adverse Event requiring suspension of the drug, the patient can suspend the study treatment. If a patient experiences an Adverse Event requiring suspension of medication, the study treatment can be suspended for 56 days from the last dose. If the study drug is discontinued for more than 56 days due to an Adverse Event, the investigator can discuss with the medical monitor based on the overall risk-benefit assessment and resume the study drug with the approval of the medical monitor. If the patient has discontinued the drug for more than 56 days and the investigator judges that the risk of continuing to give the study drug therapy is greater than the benefit, the study treatment should be permanently discontinued and the treatment end/early withdrawal visit will be conducted as described in SoA. In cases where the suspension of medication due to unforeseen non-adverse events such as force majeure reaches or exceeds 56 days, the investigator can discuss with the medical monitor after assessing the overall risk-benefit, reach a consensus with the medical monitor, and resume the study drug with the approval of the medical monitor.

Treatment with the investigational drug may cause irAEs, such as immune-related hepatitis, pneumonia, Colitis, Pancreatitis, and endocrine disorders (Thyroid function decreased, hyperthyroidism, Adrenal cortex insufficiency, Hyperglycaemia, or Diabetes mellitus). The investigational drug should be interrupted or permanently discontinued according to the severity of the event and Symptomatic treatment, such as glucocorticoids, should be given.

If the patient needs to taper the dose of steroid after receiving treatment for AE, JS001 can be

withheld for more than 56 days after the last dose, until the steroid is tapered or the dose is tapered to prednisone ≤ 10 mg/day (or equivalent dose), the acceptable duration of dose withholding must be agreed by the investigator and medical monitor.

The investigator must discuss any decision to permanently discontinue the drug in advance with the sponsor or the sponsor's authorized medical monitor and document the outcome of the discussion.

Please refer to the JS001 Investigator's Brochure for more details on dose adjustment of JS001.

6.3.2 Dose adjustment of cetuximab

The following recommendations for dose adjustments of cetuximab are provided (only applicable to the initial dose group, and can be adjusted according to the confirmed RP2D), and investigators can also refer to the package insert or local clinical practice for adjustments.

- Dose modification for infusion related reactions including an Allergic reaction

| Severity | Dose adjustment of cetuximab injection |
|---|---|
| | Within 15 minutes after the first infusion |
| Any Grade | Stop infusion<br>Risk benefit evaluation should be conducted prior to subsequent infusion, including consideration on whether the patient has already generated IgE antibodies |
| | 15 minutes after the first infusion and subsequent infusions |
| Grade 1 | Closely monitor and give slowly by IV infusion |
| Grade 2 | Slow infusion and immediate symptomatic treatment |
| Grade 3 or 4 | Stop the infusion immediately |

| | |
|---|---|
| | Active symptomatic treatment while discontinuing further treatment with cetuximab injection |

*Grade is based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE 2.0)

- Dose Modification for Serious Skin Reactions

| Severity | Dose adjustment of cetuximab injection |
|---|---|
| Grade 3 or 4 | Treatment interruption<br>If the reaction relieves to grade 2 or grade 2, the treatment will be resumed at a dose of 250 mg/m$^2$.<br>Stop treatment if there is no improvement. |
| Second occurrence: Grade 3 or 4 | Treatment interruption<br>If the reaction relieves to grade 2 or grade 2, the treatment will be resumed at a dose of 200 mg/m$^2$.<br>Stop treatment if there is no improvement. |
| Third occurrence: Grade 3 or 4 | Treatment interruption<br>If the reaction relieves to grade 2 or grade 2, the treatment will be resumed at a dose of 150 mg/m$^2$.<br>Stop the treatment if there is no improvement. |

*Grade is based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE 2.0)

### 6.4 Continued treatment after progression

It is possible that patients who have received immunotherapy may benefit from continuing treatment after imaging shows progression. Although the tumor increases in size, the internal tissue of the tumor may show significant necrosis or degeneration, and CT can show a decrease in density within the tumor lesion, and it is generally considered that the patient may benefit in this case. If the subject meets the following criteria and discusses with the medical monitor of the sponsor, the treatment can be continued after Disease progression (PD) as defined by RECIST 1.1:

- The investigator judges that continuation of study treatment is in the best interests of the patient and the patient does not need to start other antitumor therapy immediately;
- Ability to tolerate study treatment;

- No significant deterioration of the patient's performance status or tumor-related symptoms;
- No rapid disease progression, especially in important anatomical sites, such as Spinal cord compression;
- Before continuing the study treatment, the subject must sign the informed consent form in which the possible risks, discomforts and other treatment options are described;
- Continuation of study treatment must be reviewed and approved by the primary investigator at the study site.

Disease progression that is suspected to be pseudo-progression requires confirmation by subsequent imaging studies, and the imaging study should be performed at least 4 weeks after the discovery of disease progression or at the next scheduled time point (not more than 9 weeks), and before the end of study treatment. Patients who meet the progression criteria according to RECIST v1.1 will continue to undergo tumor evaluation until disease progression (iCPD as defined in iRECIST) or discontinuation of study treatment due to lack of clinical benefit, whichever occurs first. Once clinical progression occurs, a Physical examination and immediate imaging confirmation are required at any time, rather than waiting for the next scheduled imaging study.

Clinical benefit assessment must consider whether the subject is clinically deteriorating and whether they can benefit from continued treatment. If it is decided that the subject will continue study treatment after progression, the subject should continue to be treated, assessed, and followed up in accordance with the requirements of the study protocol.

Subjects who terminate JS001 treatment for various reasons and receive cetuximab monotherapy are not applicable to the above evaluation criteria, and it is not recommended to use cetuximab monotherapy after disease progression.

### 6.5 Concomitant treatment

Concomitant medication/treatment is any other drug/treatment administered at the discretion of the investigator based on consideration of the subject's benefit.

All concomitant medications/therapy received by the subject from 28 days prior to the first

dose of study medication to the end-of-treatment visit should be recorded in the case report form in strict accordance with the provisions of GCP. After the therapy cessation visit, only concomitant medications/therapy related to AEs should be recorded.

Drugs or vaccines that are clearly prohibited in the study protocol are prohibited throughout the study. If the subject has a concomitant disease that requires the use of a prohibited drug, the study drug therapy may need to be discontinued or the subject may need to receive the prohibited drug. The investigator needs to discuss with the sponsor. The decision on whether the subject continues to participate in the study treatment or receives the prohibited drug is finally decided by the investigator and the sponsor.

#### 6.5.1 Other anti-tumor therapy or investigational drug

When the patient is receiving the investigational treatment, he/she will not be allowed to receive other antitumor treatments that are not specifically specified in this study protocol, including modern Chinese herbal preparations approved for antitumor treatment and immunomodulators (including but not limited to interferon, interleukin-2, thymosin, etc.).

Not participating in other drug/device clinical trials.

Other systemic antitumor therapy, such as chemotherapy, molecular targeted therapy, hormone therapy, immunotherapy, biological therapy and radiotherapy, are not allowed.

Palliative treatment of locally symptomatic lesions, e.g., bone pain lesions, may be considered for local radiotherapy or surgery, but must meet the following criteria and discussion with the sponsor is recommended prior to initiation of palliative local therapy.

1) Subjects who require local treatment due to symptom exacerbation during the study must be judged by the investigator as to whether there is disease progression;
2) Cannot be effectively relieved through systemic therapy and seriously affect the life or living of the subject;
3) Lesion changes due to local therapy do not affect tumor assessments and in particular cannot be target lesions.

Patients may receive bisphosphonate treatment for metastases to bone. Palliative radiation for

small areas is allowed if bone metastases cannot be effectively controlled by systemic therapy or local analgesia. Prior to initiation of palliative therapy, discussion with the sponsor is required according to the same principles.

#### 6.5.2 vaccine

No live vaccine may be used within 4 weeks prior to the first dose. Subjects who are expected to need a vaccine during the study are not recommended to be enrolled.

#### 6.5.3 Immunomodulators and corticosteroids

Immunosuppression therapy is not allowed (except for the management of drug-related Adverse Events).

Immunostimulant therapy is not permitted (except for the management of drug-related Adverse Events).

Long-term, systematic use of corticosteroids is not allowed. Use of preventive medication for the study treatment, or history of allergy to contrast agent, is allowed. Short-term (not more than 3 weeks) use of corticosteroids for the treatment of non-autoimmune diseases (e.g., delayed allergic reactions caused by contact allergens) is allowed.

Corticosteroids are permitted as emergency use, topical application, spray inhalation, drop eye or local injection.

Systemic corticosteroids (≤10 mg/d prednisone or equivalent) at physiologic replacement doses (e.g., adrenal replacement steroid doses) are allowed.

#### 6.5.4 Hematopoietic growth factors and blood transfusion

Use of hematopoietic stimulating factors (e.g., granulocyte colony-stimulating factor, erythropoietin, thrombopoietin, etc.), blood transfusion, and blood products (e.g., Albumin, etc.) as a Primary prevention measure is not allowed, but is allowed for treatment of Adverse Events.

#### 6.5.5 Anti-inflammatory and Analgesic therapy

Antiinflammatory therapy may be administered if there are no known or predictable drug interactions and it is not prohibited in the protocol.

Patients with uncontrolled tumor-related pain are not recommended. Patients requiring analgesic treatment must have a stable analgesic treatment regimen prior to enrollment; symptomatic lesions suitable for palliative radiation (e.g., metastases to bone or metastasis involving nerves) should be treated at least 4 weeks prior to enrollment; asymptomatic metastatic lesions, if further growth may lead to functional impairment or refractory pain (e.g., extradural metastasis without spinal cord compression), should be considered for local/regional treatment prior to initiation of study treatment if appropriate.

### 6.6 **Drug management, distribution, recovery and destruction**

The study drug (IMP) in this study, Toripalimab Injection (JS001) and Irinotecan Hydrochloride Injection (Erbitux), was provided by the sponsor. The site was required to confirm the shipping conditions and contents when receiving IMP. All damaged goods were replaced.

All unused study drugs will be stored in the designated storage location at the clinical pharmacology site of the study center according to the specified storage conditions (2 ~ 8 °C, light protection).

The study drug should be prepared by qualified personnel according to the Study Drug Manual.

The investigator or study authorized personnel should record the date and amount of medication administered to each patient. The sponsor will arrange for authorized personnel to recover used study drug vials at the study site on a regular basis. If the drug is lost or damaged, the incident should be recorded in detail. If the drug needs to be destroyed at the study site according to the standard operating procedures of the study site, the investigator must ensure that the destruction complies with the applicable provisions of applicable environmental regulations, unit policies, etc. and provide relevant procedures for destruction. Prior to destruction, the study site must obtain written permission from the sponsor, and all destructions must be documented.

# 7 TREATMENT WITHDRAWAL OR STUDY WITHDRAWAL AND STUDY TERMINATION

## 7.1 Discontinuation of study treatment

Termination of study treatment does not mean withdrawal from the study. The subjects who have discontinued the study treatment must continue to complete the remaining study visits as required in the protocol. The subjects must discontinue the study treatment in any of the following cases:

- Subjects required to discontinue investigational drug therapy;
- The efficacy evaluation meets the criteria for disease progression, unless the subject meets the criteria for continuation of treatment after progression (see Section 6.4);
- Pregnancy during the study;
- Emergence of any clinical Adverse Event, Laboratory test abnormal, or other medical condition that would preclude the benefit of continued study treatment of the subject;
- General deterioration of health status, unable to continue participation in the study;
- Significant protocol deviations such as subject ineligibility and noncompliance were found after enrollment;
- Study termination by the Sponsor;
- Other reasons that are considered by the investigator as inability to continue study treatment.

## 7.2 Criteria for withdrawal from the study

Reasons for withdrawal of patients from the study may include:

- Withdrawal of informed consent for continued study participation and refusal of further follow-up;
- Other cases that the investigator considers necessary to withdraw from the study, such as loss of the freedom of expression of the voluntary will due to imprisonment or isolation,

or significant protocol violation;

- Lost to follow-up;
- Death of the subject;
- Study terminated by Sponsor.

The reason for withdrawal must be recorded in the case report form and the subject's medical records.

It should be noted that withdrawal of informed consent refers to the withdrawal of consent to further contact with the subject or the withdrawal of consent to further provide information by the person previously authorized. As long as possible, the subject should notify the investigator in writing that he/she has decided not to agree to follow-up. The investigator should try to explain and document the withdrawal of informed consent, which is not agreement to receive study medication or not agreement to comply with the visits specified in the study protocol.

### 7.3 Exit or termination steps

Every effort should be made to complete the efficacy and safety evaluations at the time of withdrawal from the trial as specified in the protocol, and to complete the safety follow-up period, and Adverse Events (AEs) and outcomes should be fully recorded. Investigators may recommend or provide new or alternative therapies to subjects based on their actual conditions. Non-progressive subjects should continue follow-up and imaging evaluations for as long as possible until they start new anti-tumor therapy or Disease progression.

In contrast to subjects who withdraw consent and withdraw from the study, subjects who request to discontinue study treatment will remain in the trial and will be followed up in accordance with the study procedures specified in the protocol.

If a subject refuses to attend further visits, every effort should be made to continue to follow their survival status unless the subject withdraws consent to disclose further information or to be contacted further. In this case, no further study assessments should be made and no further data should be collected.

### 7.4 Lost to follow-up

If a subject fails to return to the institution for follow-up as planned for multiple times, and the study site is unable to contact the subject, the subject will be considered as lost to follow-up.

If a subject does not return to the site for follow-up, the following actions must be taken:

1. The site must attempt to contact the subject and reschedule the missed visit as soon as possible, explain to the subject the importance of following the visit schedule, and determine whether the subject wishes to and/or should continue in the study.

2. Prior to the subject being considered lost to follow-up, the investigator or designee must make every effort to re-establish contact with the subject. These attempts should be documented in the subject's medical record.

When a patient cannot be contacted, he/she is considered to be withdrawn from the study.

### 7.5 Early termination or suspension of study

The study may be prematurely terminated or suspended if the reason is sufficient. This may be due to the decision of the regulatory authority, the change of the ethical committee's opinion, the efficacy or safety of the study drug, or according to the sponsor's judgment. In addition, the sponsor reserves the right to stop the development of the study drug at any time. The party that decides to suspend/terminate the study will issue a written notification, record the reason for termination or suspension of the study to the investigator, the sponsor and the regulatory authority. The investigator should immediately notify the ethical committee and the sponsor and provide relevant reasons.

Reasons for early termination or suspension of the study may include:

- Unanticipated, significant or unacceptable risk to subjects;
- Available efficacy results support early termination of the study;
- Study drug therapy is confirmed to be ineffective;
- Significant protocol errors were found during the study;

- Due to reasons such as serious lag in patient enrollment or frequent protocol deviations, it is very difficult to complete the study and the protocol compliance is low;
- Incomplete data or undetectable;
- Change of the sponsor's development strategy of the study drug;
- The results of the study are not of any use.

Once the safety of the study drug, protocol compliance, and data quality issues that led to study suspension are resolved and agreement is reached by the sponsor, ethics committee, or regulatory authorities, the study can proceed.

# 8 STUDY PROCEDURES AND ASSESSMENTS

## 8.1 Informed Consent Form

Patients must sign the written informed consent form before screening procedures specified in this study can be performed. Prior to signing informed consent, tumor imaging and Laboratory test required for routine clinical care, and existing tumor tissue biopsy results can be obtained if they are within the specified window period.

## 8.2 Medical history and demographic data

Previous medical history includes tumor history and history of other concomitant diseases.

- Tumor diagnosis should include: histological diagnosis results, pathological typing, histological grading, clinical stage and time of initial diagnosis before enrollment.
- History of tumor treatment: It should include the history of tumor surgery (including the history of surgery of primary tumor and metastatic tumor):
  - ✓ Operation name and date;
  - ✓ History of radiotherapy: radiotherapy site, dose, start and end dates;
  - ✓ Chemotherapy history (including neoadjuvant/adjuvant chemotherapy): chemotherapy regimen, cycles, start and end time;
  - ✓ Patients with Oropharyngeal cancer, whether there is a previous Certificate of

Analysis of HPV16 test.

- ✓ Time to disease progression or relapse after the last systemic therapy.

List concomitant medications/therapy from 28 days prior to the first study dose through the therapy cessation visit. Concomitant medications/therapy related to AEs should be recorded after the therapy cessation visit.

Demographic data included sex, birth date, and ethnicity.

### 8.3 Physical examination

A complete physical examination (general condition, head and face, skin, lymph nodes, eyes, ears, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system and mental status, etc.) will be performed within 7 days before the first dose and at the Therapy cessation visit; a targeted physical examination will be performed as clinically indicated prior to each dose and at the first follow-up visit during the safety follow-up period.

### 8.4 Vital Signs

Including pulse, respiratory rate, body temperature and blood pressure

### 8.5 Laboratory test

The collection and testing of the following samples will be performed in the local laboratory at each study site:

- 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 (GPT), aspartate aminotransferase (Glutamic-oxaloacetic transferase), gamma-glutamyltransferase (Γ-GT), total bilirubin (Bilirubin total), direct bilirubin (Bilirubin direct), alkaline phosphatase (Alk phos), blood urea nitrogen (BUN) or urea (preferably blood urea nitrogen), total protein (Protein total), albumin (Albumin), creatinine (Cr), glucose (GLU), K+, Na+, Ca2+, Mg2+, Cl- and the like;

- Coagulation function: activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB) and international normalized ratio (INR);
- Routine urinalysis: White blood cells, red blood cells, Protein urine;
- Thyroid function: Serum thyroid stimulating hormone (TSH), free triiodothyronine (FT3), Thyroxine free (FT4); if FT3 and FT4 are not available, T3 and T4 can be used instead;
- Virology test: HBsAg, HbsAb, HBeAg, HBeAb, HBcAb, HBV DNA (quantitative test of HBV DNA is required for patients with HbsAg+ and/or HbcAb+), HCV-AB (quantitative test of HCV-RNA is required if positive), and HIV-AB;
- Pregnancy test: Applicable to women of childbearing age, serum pregnancy test. Performed within 72 hours before the first dose.

### 8.6 Tumor Imaging Examination

Tumor imaging: enhanced CT or MRI of the head, neck, chest, and abdomen. Brain MRI is used for brain metastases that cannot be diagnosed with CT. Enhanced CT of the pelvis is used for subjects with suspected pelvic metastases. Bone scan is performed only when clinically indicated and must be performed within 42 days prior to the first dose. If clinically indicated, appropriate methods may be used to examine any other known or suspected disease site.

During the screening period, tumor evaluation can be based on the imaging results obtained within 4 weeks prior to the first dose of the study drug and prior to signing the informed consent, as long as they meet the requirements of RECIST 1.1.

During the study treatment period, imaging examination will be performed once every 6 weeks (±7 days) in the first 12 months, and then once every 9 weeks (±7 days) thereafter. When a subject withdraws from the study for any reason, imaging examination is required at the treatment discontinuation visit (if the time from the previous examination to the treatment withdrawal is not more than 4 weeks, no re-examination is required at the time of withdrawal). The conditions of imaging examination should be the same as those at baseline (including scanning slice thickness, contrast agent, etc.). Imaging examination is allowed with a window period of ±7 days, and unscheduled imaging examination may be performed when disease progression is suspected (e.g., symptoms deteriorate).

Subjects without radiographic progression at safety and survival follow-up should still be evaluated by imaging as frequently as possible until Disease progression, initiation of alternative anti-tumor therapy, withdrawal of consent, loss to follow-up, or death.

### 8.7 12-lead Electrocardiogram and Echocardiogram

12-lead Electrocardiogram: Prior to the first dose of study drug within 7 days, on Day 1 of each cycle (if Electrocardiogram is performed within 7 days prior to the first dose of study drug in the screening period, Electrocardiogram is not required prior to the first dose of study drug), and at the Therapy cessation visit.

Echocardiogram: performed within 7 days prior to the first dose and at the Therapy cessation visit, and as clinically indicated during the study.

### 8.8 Pharmacokinetic blood collection

The blood collection time points for subjects participating in the phase Ib study are as follows:

The concentrations of cetuximab and JS001 were determined within 0.5 h before administration of Cycle 1 and Cycle 3 D1, immediately after the end of administration of JS001 (within 10 min, only JS001 was determined), immediately after the end of administration of cetuximab (within 10 min), 2 h (±5 min), 6 h (±15 min), 24 h (±1 h), 48 h (±2 h), 96 h (±2 h), 168 h (±8 h, before the second administration of cetuximab) after the end of administration of JS001, 336 h (±12 h, before the third administration of cetuximab), 504 h (±24 h, before the next cycle administration), immediately after the end of administration of JS001 in Cycle 2 D1 (within 10 min, only JS001 was determined), and immediately after the end of administration of cetuximab (within 10 min).

4 mL of blood will be collected at each blood collection point (only 2 mL of JS001 point collection is performed) , see the Laboratory Manual for specific handling.

### 8.9 Immunogenicity Evaluation Blood Collection

6 mL whole blood samples will be collected each time (3 mL for each time if single drug is determined) for determination of anti-drug antibody (ADA) and trough concentation of JS001 and cetuximab specified in SoA. The samples will be collected prior to the first dose, prior to

administration of D1 in Cycle 2 and Cycle 4, and once every 12 weeks thereafter for one year, and then once every 24 weeks from the second year (on the day of administration and prior to administration) until therapy cessation or end of study, to evaluate the potential relationship between immunogenicity and pharmacokinetics, safety and efficacy. (See Laboratory Manual for details)

## 8.10 Collection of Tumor Tissue Samples and Biomarker Testing

Patients should provide tumor tissue samples. Fresh specimen (preferred) or formalin-fixed, paraffin-embedded tumor tissue blocks or unstained tumor specimen sections, at least 8 unstained sections (for patients with oropharyngeal cancer, if HPV16 test results are not available, 2 additional sections should be provided). 2 mL of whole blood will also be collected for sequencing paired testing. Except for patients in Phase II Cohort B, who must provide a qualified tumor tissue sample for PD-L1 testing, patients who cannot provide a qualified tumor tissue sample may also be enrolled after discussion and agreement by the investigator and the sponsor. Tumor samples must have good quality in terms of tumor content and viable tumor tissue content. Cytological smears of pleural effusion or tumor tissue from metastases to bone are not recommended. Samples should be sent to the central laboratory for testing of the following markers:

- PD-L1 expression: the antibody used for PD-L1 detection was JS311, an anti-PD-L1 monoclonal antibody developed by Junshi.
- HPV 16 (applicable only to Oropharyngeal cancer)
- Tumor mutation burden (TMB): Tumor tissue will be tested using whole-exome sequencing (WES) technology to confirm the tumor mutation burden.

## 8.11 Study Procedures

### 8.11.1 Screening Period

The screening period starts from the signing of the informed consent form and ends with the start of the first dose of the study drug or failure of screening.

The following procedures should be completed within 28 days prior to the start of Drug therapy: acquisition of the patient's signed written informed consent, collection of demographic data, measurement of height, collection of previous medical history and treatment history, collection of HPV16 status (only applicable to Oropharyngeal cancer, if previous examination has been performed), virology examination, collection of tumor tissue samples (except for patients in Phase II Cohort B who must provide qualified tumor tissue samples for PD-L1 testing), tumor imaging examination, recording of Adverse Event, recording of concomitant medications/concomitant therapies.

All the examinations below should be completed within 7 days prior to the start of study drug therapy: body weight, ECOG PS, vital signs, complete physical examination, blood routine, urine routine, blood biochemistry, coagulation function, thyroid function, 12-lead Electrocardiogram, Echocardiogram, pregnancy test (for women of childbearing potential, within 72 hours prior to the first dose, serum pregnancy test).

#### 8.11.2 Treatment Period

The following assessments should be completed on Day 1 of each cycle (C1D1) before administration: weight, ECOG score, vital signs, Physical examination, hematology, urinalysis, blood biochemistry, coagulation function, thyroid function, 12-lead Electrocardiogram, recording of Adverse Event, immunogenicity blood sampling (if applicable), and recording of concomitant medications/therapy.

For Laboratory tests (hematology, urinalysis, blood biochemistry, coagulation function, thyroid function) and Electrocardiogram on Day 1 of Cycle 1, if the corresponding screening tests have been performed within 7 days before the first dose, they do not need to be repeated.

In addition, the following procedures should also be completed on Cycle 1 Day 1 (C1D1): pharmacokinetic blood collection and immunogenicity blood collection.

On Days 8 and 15 of each cycle, the following assessments and procedures should be completed: weight, ECOG score, vital signs, Physical examination, pharmacokinetic blood collection (if applicable), immunogenicity blood collection (if applicable), recording of Adverse Events, and recording of concomitant medications/concomitant therapy.

Tumor imaging: Imaging examination will be performed every 6 weeks (±7 days) within 12 months after the start of treatment, and then every 9 weeks (±7 days) thereafter; imaging examination should also be performed at appropriate time points if new lesions are suspected. When the subject is withdrawn from the study for any reason, imaging examination should be performed at the therapy cessation visit (if the time of the previous imaging examination is not more than 4 weeks from the withdrawal date, no imaging examination is required at the time of withdrawal). The conditions of imaging examination should be the same as baseline (including scanning layer thickness and contrast agent, etc.). The imaging examination allows a window period of ±7 days, and unscheduled imaging examination can be performed when disease progression is suspected (such as symptoms worsening). The timing of imaging examinations is calculated according to calendar days and is not adjusted due to the delay in the start of the cycle. In addition to disease progression confirmed by imaging, subjects who end the study treatment for other reasons should also undergo imaging examinations at the frequency specified in the protocol until documented disease progression, initiation of new anti-tumor therapy, withdrawal of informed consent, loss to follow-up, or death.

#### 8.11.2.1 Therapy cessation Visit

The following safety evaluations and procedures should be conducted ±7 days when making a decision for treatment withdrawal and/or withdraw from the study. If the relevant tests for the safety evaluation are completed within 7 days before treatment withdrawal, the tests do not need to be repeated at this stage.

The items to be completed at the therapy cessation visit include: weight, ECOG score, vital signs, comprehensive physical examination, blood routine, urine routine, blood biochemistry, coagulation function, thyroid function, 12-lead Electrocardiogram, Echocardiogram, Pregnancy test, tumor imaging examination, PK/ADA blood collection, recording of Adverse Events, and recording of concomitant medications/concomitant therapy.

Note: tumor imaging examination: when a subject withdraws from the study for any reason, imaging examination is required at the treatment termination visit (if the previous examination is performed within 4 weeks of therapy cessation, the examination is not required again at the time of withdrawal). In addition to disease progression confirmed by imaging, subjects who end study

treatment for other reasons should also be subjected to imaging examination at the frequency specified in the protocol until disease progression is documented, new anti-tumor therapy is initiated, the subject is lost to follow-up, or death.

#### 8.11.3 Follow-up period

##### 8.11.3.1 Safety follow-up period

Follow-up will occur every 30 days (±7 days) from the last study treatment until 60 days after the last study treatment or initiation of new anti-tumor therapy, whichever occurs first. Survival information, Adverse Events, and concomitant medications/concomitant therapies associated with Adverse Events will need to be collected. The above information can be collected through an effective method such as a telephone visit.

In addition to Disease progression confirmed by imaging, subjects who end the study treatment for other reasons should also undergo imaging examination as frequently as possible as specified in the protocol until Disease progression is documented, new anti-tumor therapy is initiated, the subject is lost to follow-up, or the subject dies.

##### 8.11.3.2 Survival follow-up period

After the safety follow-up period, subjects entered the survival follow-up period. The survival follow-up period ended when the subject died, was lost to follow-up, withdrew consent and refused to continue to provide information, or the sponsor terminated the study. During this period, a visit was made by a valid method such as telephone follow-up once every month to collect survival information and subsequent anti-tumor treatment information (if the subject started new anti-tumor therapy, the treatment regimen and start and end dates should be recorded).

For subjects without radiographic evidence of disease progression, they should continue to undergo imaging evaluation at the frequency of efficacy evaluation specified in this study until disease progression, death, loss to follow-up, withdrawal of consent and refusal to provide additional information, initiation of other anti-tumor therapy, or termination of the study by the sponsor, and the radiographic evidence of disease progression in such subjects should be obtained whenever possible.

Only SAEs related to study drug JS001 were recorded.

#### 8.11.4 Unscheduled Visit

If the subject needs unscheduled follow-up due to Adverse Event during the trial, the following items should be recorded:

- Record concomitant medication/concurrent treatment;
- Recording of Adverse Events;
- Document any pertinent tests (including imaging, if any).

### 8.12 **Efficacy Assessments**

#### 8.12.1 Efficacy evaluation indicators

The efficacy variables included objective response rate (ORR), duration of response, best response rate, disease control rate, progression-free survival and overall survival.

Objective Response Rate (ORR): Percentage of subjects who have received the study treatment and have the best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1 and iRECIST criteria.

Duration of Response (DoR): defined as the time from the date of the first recorded tumor response (assessed as CR or PR according to RECIST 1.1 and iRECIST criteria, respectively) to the date of the first recorded objective tumor progression or death from any cause (whichever occurs first).

Best overall response (BOR) is defined as the best response recorded in the best overall response evaluation. For patients who have no documented progression or start subsequent antitumor therapy, the best overall response is determined based on all the responses recorded.

Disease control rate (DCR): The proportion of subjects who received study treatment and had the best overall response (BOR) of complete response (CR), partial response (PR) and stable disease (SD) as evaluated by RECIST 1.1 and iRECIST criteria, respectively.

Progression-free survival (PFS): defined as the time from enrollment to the date of the first documented Tumour 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.

8.12.2 Efficacy evaluation criteria

Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and duration of response (DoR) based on RECIST 1.1 and iRECIST criteria will be evaluated by imaging methods.

Survival time will be recorded and evaluated. The survival status will be followed up every 1 month after the subject is discharged from the group, through telephone follow-up and other effective visits, until death, loss to follow-up, withdrawal of informed consent, or termination of the study by the sponsor.

Evaluation of tumor response will include all known or suspected sites of disease. Computerised tomography (CT) or magnetic resonance imaging (MRI) scans of the head, neck, chest, and abdomen; contrast-enhanced CT of the abdomen and pelvis for suspected pelvic metastases; brain MRI for brain metastases when not confirmed by CT; and bone scan only when clinically indicated. Appropriate methods may be used to evaluate any other known or suspected sites of disease at the discretion of the Investigator.

The imaging evaluation at screening was performed within 28 days prior to the first dose of the investigational drug. The first tumor imaging evaluation should be performed 6 weeks (±7 days) after the start of study treatment. During the study treatment, it was performed once every 6 weeks (±7 days) within the first 12 months, and then once every 9 weeks (±7 days) thereafter, until Disease progression, loss to follow-up, death, withdrawal of informed consent, initiation of other anti-tumor therapy by the subject, or termination of the study by the sponsor.

If the efficacy reaches complete response (CR) or partial response (PR), the subject must be re-examined to confirm not less than 4 weeks (28 days) after the first evaluation.

The same imaging technique used in the screening period should be used for the same type of lesion in subsequent tumor evaluations. The evaluation of anti-tumor activity will be performed through radiographic imaging in the screening period and during treatment according to the trial flow chart; evaluation should also be performed when progressive disease is suspected (e.g., worsening of symptoms) and when the subject withdraws from the study (if not completed in the

previous 4 weeks). Once clinical progression occurs, the subject should undergo a physical examination at any time and radiographic confirmation should be performed immediately rather than waiting for the next scheduled imaging. If the unscheduled imaging examination at this time reveals clinical progression that does not meet the criteria for disease progression according to RECIST v1.1, subsequent examinations should still be performed on the scheduled date of the next imaging examination, unless the next scheduled examination is less than 14 days from this examination.

All patients should continue to have tumor evaluation according to the study protocol, regardless of medication interruption or delay in medication. If a patient needs to discontinue study treatment due to general worsening of health status, but there is no objective evidence of disease progression at this time, it should be reported as symptoms worsening. Even after discontinuation, every effort should be made to record objective disease progression (e.g., radiological confirmation).

Prior to administration in the next cycle, the investigator must review the results. Disease progression suspected of pseudo-progression requires confirmation in subsequent imaging examinations, which must be performed at least 4 weeks after the detection of disease progression or at the next scheduled time point (not more than 9 weeks), and before therapy cessation. Patients who meet the progression criteria according to RECIST v1.1 will continue to receive tumor evaluation until re-progression (iCPD as defined in iRECIST) or the end of study treatment due to no clinical benefit, whichever occurs first.

Documents and images of all subjects must be source verified and peer reviewed.

### 8.13 Safety Evaluation

Please see SoA for the schedule of all safety assessments.

The Investigator must review the test reports, conduct a record review, and record any clinically significant changes that occur during the study in the AE section of the CRF. The test reports should be archived in source files.

If results of non-protocol-specified laboratory evaluations performed at the site laboratory lead to a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), the results must be recorded in the CRF.

8.13.1 Safety Evaluation Measures

Safety assessments will include monitoring and recording of Adverse Events, including serious Adverse Events, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and performing other protocol-specified tests that are critical to the safety assessment of the study.

8.13.1.1 Adverse Event

An Adverse Event is any untoward medical occurrence in a patient during the course of a clinical study in which the patient was being treated with a pharmaceutical product, as defined in 45 CFR 46.101(b)(5), whether or not considered related to the drug product. Adverse Events can be any of the following:

1) Worsening of pre-existing (prior to clinical trial) medical conditions/diseases (including worsening of symptoms, signs, laboratory abnormalities; except those clearly related to disease progression, see Section 8.13.2.4.4);

2) Any new Adverse Event: any new adverse medical condition (including symptoms, signs, newly diagnosed diseases);

3) Clinically significant abnormal laboratory test values or results that are not due to concomitant diseases.

Investigators should record in detail any Adverse Events that occur in subjects, including: description of Adverse Events and all relevant symptoms, occurrence time, severity, cause of Adverse Events, correlation with the investigational product, duration, measures taken, final results and outcome.

The name of the Adverse Event should be recorded on the CRF as the name of the diagnosis or disease. If the name of the Adverse Event cannot be specified or the investigator considers that the name of the diagnosis or disease cannot be used as the name of the Adverse Event, the clinical condition or symptom will be recorded as the name of the Adverse Event on the CRF.

8.13.1.2 Serious Adverse Events (report to the sponsor within 24 hours of awareness)

A serious Adverse Event is an Adverse Event that meets one or more of the following criteria:

- Results in death
- Life threatening (i.e., the event places the patient at an immediate risk of death)
  Note: "Life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event that might have caused death if it were more severe.
- Requires Hospitalisation or prolongation of existing hospitalization
- An event that results in permanent or significant disability/incapacity/incapacity (i.e., an AE that causes substantial harm to the patient's ability to perform normal activities)

Note: The term "disability" refers to a substantial disruption of a person's ability to perform normal life functions. This definition does not include events of relatively minor clinical significance, such as simple headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., Ankle sprain), which may affect daily function but do not result in a significant loss of function.

- Teratogenicity and Birth defects
- Other Significant Medical Events: Significant Medical Events may not be immediately life-threatening or result in death, hospitalization, incapacity or loss of function but may, based upon appropriate medical and scientific judgment, contribute to patient risk or may require intervention to prevent one of the serious consequences listed in the definition above.

**Explanation for SAE Waiver:**

- Death due to disease progression is an efficacy endpoint, and it is not necessary to report it as an SAE. See Section 8.13.2.4.4;
- The following specific hospitalizations and prolonged hospitalizations do not need to be reported as SAEs:
  - Hospitalization for visits specified in the protocol during the clinical trial, without new Adverse Events and exacerbation of pre-existing diseases (e.g., operations and administration of study drugs as required by the protocol; when hospitalization is planned for scheduled visits, routine clinical treatment for Laboratory test abnormalities of CTCAE grade 1-2 is not considered to be the cause of prolonged

hospitalization, and should be reported as non-serious AE according to the AE definition);

- Elective hospitalization not associated with worsening of Adverse Events (eg, elective surgery);
- Hospitalization for administrative reasons (eg, routine annual physical examination);
- Hospitalization for reasons such as medical insurance reimbursement (such as Common cold, regulation, and other routine conditions that do not require hospitalization).

8.13.1.3 Adverse Events of special interest (report to the sponsor within 24 hours of awareness)

Adverse Events of special interest (AESIs) must be reported immediately by the investigator to the sponsor (i.e., no more than 24 hours after awareness of the event). The Adverse Events of special interest in this study include:

· Immune-related Myocarditis

· Abnormal hepatic function meeting Hy's law, ALT or AST elevation (> 3 × ULN) combined with Bilirubin total elevation (> 2 × ULN) or clinical jaundice, excluding cholestatic jaundice or other causes of elevated Bilirubin.

8.13.2 AE/SAE Recording and Reporting

The Investigator is responsible for ensuring that all Adverse Events are recorded on the Adverse Event page of the eCRF and reported to the Sponsor as outlined in this section.

For each Adverse Event recorded on the eCRF form, the investigator will assess seriousness, severity, and causality.

8.13.2.1 Reporting Period of Adverse Events

Investigators should ask each patient and his/her contact for information on Adverse Events. All Adverse Events, whether reported by the patient or recorded by the investigator, should be recorded in the patient's medical record and eCRF for Adverse Events.

After the patient signs the informed consent form and before the start of study drug administration, only all SAEs will be recorded and reported. After the start of study drug administration until the end of the safety follow-up period (60 days after the last dose of study drug) or the start of a new anti-tumor therapy (whichever occurs first), all AEs (regardless of the relationship with the study drug) will be recorded and reported, and all SAEs, AESIs, and pregnancies will be reported. Thereafter, the investigator will not actively collect AEs, but should still report SAEs that are considered to be related to previous treatment with JS001 to the Sponsor's Drug Safety Department.

#### 8.13.2.2 Assessment of Severity of Adverse Events

The severity of Adverse Events will be assessed using the NCI CTCAE (version 5.0) grading scale for Adverse Event severity. The severity of Adverse Events not specifically listed in the NCI CTCAE criteria will be assessed according to Table 4.

**Table 4 Severity Grading Scale for Adverse Events Not Clearly Listed in the NCI CTCAE4**

| Grade | Severity |
|---|---|
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observation only; or intervention not indicated |
| 2 | Moderate; minor, local or requiring non-invasive interventions; or adequate age-appropriate tools limited instrumental activities of daily living |
| 3 | Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting activities of daily living |
| 4 | Life-threatening or requiring urgent intervention |
| 5 | Adverse Event-Related Deaths |

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the latest version of NCI CTCAE criteria (version 5.0), see:

#### 8.13.2.3 Adverse Event causality assessment

The investigator is obligated to assess the causal relationship between the study drug and Adverse Events. 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 occurrence of the event, and any alternative causes, etc. (related/unrelated), i.e., there is a reasonable correlation between the Adverse Event and the study drug, and 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, etc.

The following factors should be taken into consideration when determining the correlation:

- Temporal relationship between the occurrence of the event and the start of administration of study drug
- The course of the event, with special consideration of the effects of dose reduction, discontinuation of the investigational drug, or reintroduction of the investigational drug (if applicable)
- Known correlation between the event and the drug or similar therapy
- Known correlation between the event and the disease under study
- Presence of risk factors or use of concomitant medications known to increase the incidence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event
- If there is evidence that the causal relationship of the case is "plausible", the causal relationship can be determined as "relevant". In general, a causal relationship of "plausible" refers to a causal relationship that is suggested by facts (evidence) or laboratory parameters. In the case of limited information, investigators should give a reasonable causal relationship judgment based on available evidence as much as possible, rather than record "unable to judge".

| | |
|---|---|
| Definitely Not Related | The study drug was not used, or there was no reasonable correlation between the time of study drug use and the occurrence of AE, or there was another clear cause of the AE. |
| Unlikely Related | There is a temporal relationship between the occurrence of the study drug or AE and the use of the study drug, but there is another plausible explanation for the AE. Dechallenge is negative or unclear. |
| Possibly related | There is a reasonable temporal relationship between the occurrence of the study drug administration and the occurrence of the AE, but there is also some other etiology for the AE. Positive dechallenge. |
| Probably related | There is a reasonable temporal relationship between the occurrence of the study drug and the onset of the AE, and the AE is more reasonably explained by the study drug rather than other causes. Positive dechallenge. |

| | |
|---|---|
| Definitely related | There is a reasonable temporal relationship between the occurrence of the study drug administration or AE and the use of the study drug, and the AE is more reasonably explained by the study drug than by other causes. Positive dechallenge and rechallenge (if possible). |

- The record rule for the reasonable correlation of EDC is:
- Reasonable correlation refers to “definitely related”, “probably related”, and “possibly related”;
- No reasonable correlation refers to ' unlikely Related ' and ' definitely not Related '.

#### 8.13.2.4 Adverse Event Documentation Procedures

When documenting Adverse Events on the Adverse Event eCRF, investigators should use the correct medical terminology/concepts. Avoid colloquialisms and abbreviations.

Only one Adverse Event term should be recorded in the Event field on the Adverse Event eCRF.

##### 8.13.2.4.1 Serious Adverse Event

SAEs should be reported from the time the patient signs the informed consent form until the end of the safety follow-up period. Any SAE occurring after the end of the safety follow-up period should be reported to the Sponsor's Drug Safety Department only if the investigator considers the event to be causally related to the study treatment drug JS001.

The investigator should complete the standard SAE Report Form provided by the sponsor in accordance with the filling guide within 24 hours after learning of an SAE and send it to the email address provided by the sponsor, so that the sponsor can process the relevant SAE in its safety database, and report cases of suspected unexpected serious adverse reactions (SUSARs) within the regulatory time limit.

The symptoms, severity, correlation with the investigational drug, occurrence time, treatment time, measures taken, follow-up time and method, and outcome of SAE should be recorded in detail. If the investigator believes that an SAE is unrelated to the investigational drug but potentially related to the study conditions (e.g., discontinuation of the original treatment, or comorbidities during the trial), the relationship should be detailed in the narrative section of the SAE report form.

If any of the following important information of an ongoing SAE changes, the investigator should submit a follow-up report immediately within 24 hours after awareness:

- New sign or symptom or diagnostic change;
- Important new diagnosis or test results;
- Change of causality based on the new data;
- Change in the outcome of event, including recovery;

If the investigator considers that the information of previously reported SAEs is misreported, he/she can make a correction, withdrawal or downgrade in the follow-up report, and report as per the SAE reporting procedure.

The investigator should promptly clarify the medical queries raised by the sponsor about SAEs.

8.13.2.4.2 Adverse Events of special interest

AESIs, as specified in the clinical study protocol, must be reported immediately by the investigator to the sponsor, regardless of seriousness (i.e., no more than 24 hours after becoming aware of the event), to allow the sponsor to monitor in a timely manner and meet reporting requirements of other regulatory authorities.

8.13.2.4.3 Abnormal Laboratory Test Findings

Blood sample/urine sample/other samples for laboratory tests will be collected according to the study flow chart and tested in the central laboratory. Not every laboratory test abnormality is an AE, and it should be combined with baseline data and judged for clinical significance. When a laboratory test abnormality meets any of the following criteria, it must be reported as an AE:

- Is accompanied with clinical symptoms;
- Results in a change in study treatment (e.g., dose modification, Therapy interrupted, or Treatment withdrawal);
- Results in a medical intervention being required (e.g., potassium supplementation for Hypokalaemia) or a change in a concomitant medication;
- Results considered clinically significant by the investigator.

Investigators should use clinical diagnostic terms whenever possible, rather than laboratory test terms (e.g., anemia, rather than low haemoglobin). If a clinically significant laboratory abnormality is a manifestation of a disease or syndrome (e.g., elevated Alk phos and bilirubin

associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the AE page of the eCRF. If a clinically significant laboratory abnormality is not a manifestation of a disease or syndrome, the abnormality itself should be recorded on the AE page of the eCRF, with a descriptor indicating whether the result is above or below normal (e.g., “hyperpotassium” rather than “potassium abnormal”). If a laboratory abnormality can be described with a precise clinical term according to standard definitions, the clinical term should be recorded as the AE. For example, serum potassium increased to 7.0 mol/L should be recorded as “hyperkalemia”.

8.13.2.4.4 Disease progression

Disease progression is an efficacy endpoint. Disease progression refers to the worsening of the patient's condition caused by the drug therapy, i.e., advanced head and neck squamous cell carcinoma. Disease progression may be an increase in the severity of the disease and/or an increase in disease symptoms and signs. The occurrence of new metastasis or progression of existing metastasis of the primary cancer studied should be considered as disease progression rather than an AE. During the study, events due to disease progression should not be reported as AEs.

8.13.2.4.5 Death

All deaths that occur during the study treatment period or during the safety follow-up period specified in the protocol after the last study treatment must be reported as follows:

- Death due to disease progression is defined as an efficacy endpoint and does not need to be reported as an SAE, but needs to be recorded on the death description page of the eCRF.
- When death is not due to disease progression of the study disease, the AE that caused death must be reported as an SAE. The death explanation page should also be recorded in the eCRF. The report should include possible disease progression and complication explanations (if applicable) and indicate the primary and secondary causes of death.
- Unexplained deaths should always be reported as SAEs. The death description page should also be recorded in the eCRF. The investigator should follow up to learn and

assess the cause of death as much as possible. Autopsy helps assess the cause of death, and if autopsy is performed, a copy of the autopsy result should be sent to the sponsor within the normal time limit.

Deaths that occur after the protocol-specified safety follow-up period for the last study treatment should be recorded on the death page. If the death is due to an event that occurs after the protocol-specified safety follow-up period and is considered to be due to the delayed toxicity of the study drug JS001, the death needs to be reported to the sponsor as an SAE.

8.13.2.4.6 Pregnancy Event

All pregnancies from the first dose to the safety follow-up period are to be reported.

If a female patient becomes pregnant during the clinical trial, she will be withdrawn from the study, and the pregnancy will be reported to the sponsor within 24 hours after the investigator becomes aware of the pregnancy, and the Junshi Clinical Trial Pregnancy Report/Follow-up Form will be completed.

If the partner of male subjects becomes pregnant during the clinical trial, the subject will continue the clinical trial and the investigator should report it to the sponsor within 24 hours after learning of the Pregnancy of partner and fill in the Junshi Clinical Trial Pregnancy Report/Follow-up Form.

The investigator should follow up the pregnancy outcome until 1 month after delivery, and report the outcome to the sponsor.

If the pregnancy outcome is stillbirth, spontaneous abortion, foetal malformation, it will be considered as an SAE and needs to be reported according to the timeline for SAE reporting.

If a subject experiences an SAE concurrently during pregnancy, an SAE Report Form should also be completed and reported in accordance with the SAE reporting procedures.

8.13.2.4.7 Overdose

Overdose refers to accidental or intentional administration of a large and medically significant dose. In this study protocol, it is defined as an overdose of any of the study drugs exceeding 20% of the dose specified in the protocol. Adverse events due to overdose alone do not need to be

reported as AEs. If AEs/SAEs occur due to overdose, they should be recorded as AEs/SAEs; otherwise, protocol violations should be recorded only.

#### 8.13.3 follow-UP OF Adverse Events

##### 8.13.3.1 Investigator Follow-Up

The investigator should follow up all AEs until any of the following occurs:

- AE is relieved or improved to baseline level or better;
- The investigator confirms that the event is stable and no further improvement is expected;
- Death of the subject;
- The subject has lost contact or withdrawn the ICF;
- Subjects start new anti-tumor therapy.

##### 8.13.3.2 Follow-up by the Sponsor

For serious Adverse Events, attention will be paid to Adverse Events and pregnancy in particular. The sponsor or designee will follow up by telephone, fax, email and/or monitoring visits to obtain additional details and outcomes (e.g., discharge summaries, consultation reports, autopsy reports) to allow for an independent medical assessment of reported cases.

## 9 STATISTICAL CONSIDERATIONS

### 9.1 Sample Size Determination

The sample size for the Phase Ib study depends on the number of dose arms and the number of DLTs. A minimum of 12 patients will be enrolled to determine the recommended Phase II dose.

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

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 subjects are required to be enrolled in the first stage, and the cohort will be terminated if the number of effective cases is less than or equal to 5. Otherwise, 21 additional subjects are required to be enrolled until a total of 45 subjects are enrolled. At a significance level of 0.05 (2-sided) and a power of 90%, if the number of effective cases is greater than 13 out of all subjects, the null hypothesis will be rejected.

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

## 9.2 Analysis Sets

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

The safety analysis set (SS) included all patients who received any dose of toripalimab. SS was the primary analysis set for safety, immunogenicity, pharmacokinetics, and biomarker analyses.

Efficacy evaluable analysis set (EAS) includes patients who have received at least one dose of toripalimab injection and have baseline and at least one post-baseline tumor evaluation data.

PK analysis set: includes all subjects who have received at least one dose and can provide at least one valid PK assessment data.

## 9.3 General Method

Appropriate statistics will be used based on the data type: mean, standard deviation, median, minimum, and maximum for continuous data; frequency and percentage for categorical data.

Unless otherwise specified, the baseline measurement value refers to the last available data obtained prior to the first dose of the investigational drug.

## 9.4 **Efficacy analysis**

Efficacy data were analyzed based on the full analysis set and the efficacy evaluable analysis set.

### 9.4.1 primary efficacy endpoints

The primary efficacy endpoint in cohort A of this study is the objective response rate (ORR) evaluated by IRC according to RECIST1.1 criteria. It is defined as the proportion of subjects who receive study treatment and have the best overall response (BOR) of complete response (CR) or partial response (PR) as evaluated by IRC according to RECIST 1.1 criteria.

The primary efficacy endpoint in cohort B was the objective response rate (ORR) evaluated by investigators according to RECIST1.1 criteria. It was defined as the proportion of patients who received study treatment and had a best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1 criteria as evaluated by investigators. The ORR was calculated and the 95% confidence interval for ORR was calculated using Clopper-Pearson method.

### 9.4.2 Secondary efficacy endpoints

Secondary efficacy endpoints in Cohort A included ORR assessed by investigators according to RECIST 1.1, disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and 1-year OS rate assessed by investigators and IRC.

Secondary efficacy endpoints in cohort B included disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and 1-year OS rate, as assessed by investigators per RECIST1.1.

#### 9.4.2.1 Disease control rate

Disease control rate (DCR): defined as the proportion of subjects with the best overall response (BOR) as assessed according to RECIST v1.1 criteria, including complete response (CR), partial response (PR) and stable disease (SD). The analysis of DCR was performed using the same analysis method as ORR.

#### 9.4.2.2 Progression-free survival (PFS)

PFS is defined as the time from the first dose of the study drug to Disease progression or death due to any cause, whichever comes first. Kaplan-Meier method is used to estimate the median PFS, and the 95% confidence interval of median PFS is estimated by the log-log function converted Brookmeyer-Crowley method, and Kaplan-Meier survival curve is plotted.

#### 9.4.2.3 Duration of response (DOR)

DOR is defined as the time from the first assessment of CR or PR to the first assessment of PD or death due to any cause. The DOR analysis is performed using the PFS analysis method for subjects with BOR of CR or PR.

#### 9.4.2.4 Overall survival (OS)

OS is defined as the time from the first dose to death caused by any reason. The same analysis method as PFS will be used for OS analysis.

#### 9.4.2.5 1-year OS rate

The 1-year OS rate is defined as the proportion of patients who survive for 1 year after the first dose. Kaplan-Meier method is used to estimate the 1-year OS rate after the first dose, and 95% CI is calculated using the Greenwood formula.

### 9.5 Safety analysis

Safety analysis will be performed on the safety analysis set. For the Phase Ib part, safety analysis will be performed by different dose groups (if dose adjustment is made to the alternative dose group).

The exposure extent of each study drug was summarized and described based on the number of cycles of treatment received (number and percentage of patients), duration of administration (days), cumulative total dose received by each patient (mg), dose intensity, and relative dose intensity.

Adverse Events will be coded and categorized using MedDRA22.1 or above. The number and incidence of treatment-emergent adverse events (TEAEs) will be tabulated by preferred term and system organ class. In addition, serious adverse events, adverse events of grade 3 and above, adverse events related to the study drug, and adverse events leading to discontinuation or

interruption of the study drug will be summarized accordingly. Multiple occurrences of the same adverse event will be counted once according to the maximum severity. The above adverse events will be tabulated.

Deaths reported during study treatment and those reported during follow-up after treatment withdrawal will be summarized.

Descriptive statistics were used to summarize the measurements and changes from baseline at baseline and the last visit of the treatment period for Laboratory tests, Physical examination, vital signs, body weight, ECOG performance status, ECG, as well as the number and proportion of patients with abnormal changes after baseline. The measurements at each visit were listed.

### 9.6 Pharmacokinetic analysis

Based on the PK analysis set, PK concentration data were summarized and listed descriptively by drug at the protocol-specified time points. Mean and median drug concentration-time curves and semilogarithmic plots were plotted for each drug. Individual drug concentration-time curves and semilogarithmic plots were plotted for each subject according to actual sampling time. PK parameters of JS001 and cetuximab were calculated using the non-compartmental model in WinNonlin. Descriptive statistics were summarized and listed for plasma drug concentrations and PK parameters. If applicable, model-based methods will be used for exposure-response analysis.

### 9.7 Immunogenicity analysis

Descriptive statistical analysis was performed to evaluate the changes in the development of anti-toripalimab antibodies and anti-cetuximab antibodies in participants at various sampling time points after treatment.

### 9.8 Biomarker analysis

In subjects who provide tumor tissue samples, the relationship between PD-L1, HPV (Oropharyngeal cancer) and TMB and efficacy (including ORR, OS and PFS) will be explored based on the test results of PD-L1, HPV (Oropharyngeal cancer) and TMB.

## 10 DATA COLLECTION AND MANAGEMENT

### 10.1 Data Quality Assurance

Data entered manually into the eCRF via EDC by the site. The site is responsible for entering data into the EDC system. If there are discrepancies, the CRO will request clarification from the site, which will be resolved electronically in the EDC system.

The CRO will develop a data quality plan describing the quality checks that will be performed on the data. Central laboratory data will be sent directly to the Sponsor or CRO and processed by the CRO's standard procedures to complete the electronic transfer of these data.

The Sponsor will oversee the data management of this study, including approval of the CRO's data management plan and specifications. Data will be transferred electronically from the CRO to the Sponsor on a regular basis, and the CRO's standard procedures will be used to process and complete the electronic transfer of these data.

The eCRFs and correction documents will be stored in the audit trail of the EDC system. The system backup of data stored in the CRO and the record keeping of study data will be consistent with the CRO's standard procedure.

### 10.2 Electronic Case Report Form

eCRFs will be completed through the sponsor's designated EDC system. The study site will be trained and provided with the corresponding eCRF completion guidelines. eCRFs will be submitted electronically to the sponsor and processed according to the sponsor's instructions.

All eCRFs should be completed by designated, trained site personnel. They should be reviewed by the Investigator or designee and electronically signed and dated.

At the end of the study, investigators will receive a readable CD containing the patient data of their site, which must be kept together with the study records. Investigators must provide a receipt for the CD.

### 10.3 Source data records

The study monitor will perform ongoing source data verification to ensure that the critical protocol data (i.e., source data) entered by authorized site staff into the eCRF are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are the documents in which the patient data are first recorded, including but not limited to hospital records, clinical and clinic records, laboratory records, memorandums, patient self-assessment results, evaluation lists, pharmacy dispensing records, data from automated instruments, copies of transcribed records that have been verified to be accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records maintained by pharmacies, laboratories, and medical technology departments involved in the clinical trial.

Before the study starts, the types of source documents to be generated will be clearly defined in the trial monitoring plan. This includes any protocol data to be entered directly into the eCRF (i.e., no data in a prior written or electronic record) and considered as source data.

The source documents used to validate the accuracy and completeness of the data entered into the eCRF may not be deleted or destroyed and must be retained in accordance with the recording keeping procedures described in Section 10.5.

To facilitate source data verification, investigators and institutions must allow the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The research site must also allow appropriate health authorities to conduct inspections.

### 10.4 Use of Computer Systems

When clinical observations are entered directly into a site’s computerized medical record system (i.e., in lieu of original hard copy records), the electronic records may serve as source documents if the system has been validated in accordance with health authority requirements for

computer systems used in clinical studies. An appropriate computerized data collection system should maintain the original entry of the data. If the original data are modified, the system should maintain a readily accessible audit trail that shows the original data as well as the reason for the change, the name of the person making the change, and the date of the change.

### 10.5 Record keeping

Records and documents related to the conduct of this study and the distribution of IMPs, including eCRFs, ICFs, Laboratory test results, and drug inventory records, must be retained by the principal investigator for at least 5 years after completion or termination of the study or for the time required by relevant national or local health authorities, whichever is longer. The documents may then be destroyed, subject to local regulations.

No records should be destroyed prior to obtaining the Sponsor's written approval. The Sponsor should be provided with written notification prior to the transfer of any records to another party or the transfer of any records to another location.

## 11 REGULATORY AND ETHICAL CONSIDERATIONS

### 11.1 Regulatory Compliance

This study must be conducted in strict accordance with China's Good Clinical Practice, ICH E6 Guidelines for Good Clinical Practice, the Declaration of Helsinki, and relevant laws and regulations of China, whichever affords the greater protection of the individual patient. The study will be conducted in accordance with ICH E2A Guideline (Clinical Safety Data Management: Definition and Standards for Accelerated Reporting).

### 11.2 Informed Consent Process

- The Investigator or their representative will explain the nature of the study to the subject or their legal representative and will answer all questions regarding the study.
- The subject must be informed that participation is voluntary. Subjects or their legally authorized representatives will be required to sign a written informed consent in compliance with local regulations, ICH guidelines, and EC or study center requirements.

- Medical records must include a statement confirming that the subject signed written informed consent prior to enrollment with the date of the signature. The staff obtaining the informed consent must also sign the ICF.
- Subjects must be informed of and consent to the most current version of the ICF while participating in the study.
- The ICF must be provided to the subject or the subject's legally acceptable representative.

### 11.3 Institutional Review Board or Ethics Committee

The study protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to the EC/IRB and reviewed and approved by the EC/IRB prior to initiation of the study.

Any changes to the study protocol design require EC/IRB approval prior to implementation, unless the changes are essential to eliminate any potential harm to the subjects.

The investigator is responsible for:

- Submit to the EC/IRB a written summary of the progress of the study at least annually in accordance with the requirements, policies and procedures established by the EC/IRB.
- The investigator is responsible for reporting serious Adverse Events or other important safety findings to the EC as required by the EC/IRB.
- Oversee the conduct of the study in accordance with ICH guidelines, EC/IRB, and all other applicable local regulations.

### 11.4 Confidentiality

The Sponsor will code the enrolled patients to comply with confidentiality standards by assigning a unique patient identification number. This means that any patient data transmitted to the Sponsor department will not include the patient's name.

Patient medical information obtained in this study will be kept confidential and will not be disclosed to third parties except as required by law or as authorized or consented to by the patient in the informed consent (or separate authorization for use and disclosure of personal health information).

Medical information will need to be provided to the patient's personal physician or other appropriate medical personnel responsible for the patient's health for treatment purposes.

Data generated during the study must be provided to the representatives of the national and local health authorities, the sponsor's monitors, representatives and collaborators, and the IRB/EC of each study site, as applicable.

# 12 STUDY DOCUMENTATION, MONITORING, AND GOVERNANCE

## 12.1 Study records

The investigator must maintain adequate and accurate records to adequately document the conduct of the study, including, but not limited to, the protocol, protocol amendments, informed consent forms, IRB/EC documents, and government approvals. In addition, at the end of the study, the investigator will receive patient data, including an audit trail of all data changes.

## 12.2 Protocol Deviations

The investigator should document and explain any protocol deviations. The investigator should promptly report to the Sponsor and IRB/EC any deviations that may affect patient safety and Data Integrity in accordance with established IRB/EC policies and procedures.

## 12.3 Central Audits

The Sponsor or authorized representative will conduct site visits to check study data, patient medical records, and eCRFs. The investigator will allow national and local health authorities, Sponsor monitors, representatives, and collaborators; and IRB/EC to verify Facilities and records related to this study.

## 12.4 Publication and Patent

The results of this study may be published or presented at a scientific meeting. If foreseeable, the Investigator agrees to submit all papers or abstracts to the Sponsor prior to submission for publication to allow the Sponsor to protect proprietary information and provide advice.

Sponsor compliance with publication requirements. According to standard editorial and ethical practice, the sponsor typically supports publication of only complete, multicenter study

information, not single-center study data. In such cases, a coordinating investigator will be designated by mutual agreement.

The authorship will be determined by both parties and meet the requirements of the International Committee of Medical Journal Editors.

Any inventions and resulting patents, improvements and/or know-how resulting from the use of the data of this study are the exclusive property of the Sponsor, unless otherwise agreed.

### 12.5 Protocol Amendment

Protocol amendments are written by the Sponsor. Protocol amendments need to be submitted to the IRB/EC and regulatory authorities, as required by local regulatory requirements.

Prior to implementation of any changes, IRB/EC and regulatory approvals (as applicable per local requirements) must be obtained (except for changes to eliminate direct harm to patients or changes that only involve logistics or administration, e.g., change in Medical Monitor or contact information).

# 13 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 13.1 Appendix 1: Eastern Cooperative Oncology Group (ECOG) score

| Grading | Description |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work) |
| 2 | Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | Fully disabled; cannot take care of self; confined to bed or chair |
| 5 | Death |

## 13.2 Appendix 2: Cockroft-Gault formula (calculation of Creatinine clearance)

Serum creatinine concentration: mg/dL

$$\text{Creatinine clearance in men}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{(140 - \text{Age}) \times \text{Body weight}}{72 \times \text{Serum creatinine}}$$

$$\text{female Creatinine clearance}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{0.85 \times (140 - \text{Age}) \times \text{Body weight}}{72 \times \text{Serum creatinine}}$$

Serum creatinine concentration: μmol/L

$$\text{Creatinine clearance in men}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{(140 - \text{Age}) \times \text{Body weight}}{0.818 \times \text{Serum creatinine}}$$

$$\text{female Creatinine clearance}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{0.85 \times (140 - \text{Age}) \times \text{Body weight}}{0.818 \times \text{Serum creatinine}}$$

The units for age and weight are years and kilograms (kg), respectively.

## 13.3 Annex 3: Evaluation of solid tumour response (RECIST version 1.1 assessment criteria) guidelines

The text below is from the following reference: Eisenhauer EA， Therasse P， Bogaerts J， Schwartz LH， Sargent D， Ford R， et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).Eur J Cancer 2009;45:228~247.

**1 Inclusion Criteria**

Only subjects with measurable tumors at baseline can be enrolled in protocols with objective response rate as the primary endpoint.

**2 Definitions**

**Measurable disease—**At least one measurable lesion. Tumor lesions must be precisely measurable in at least one dimension (the longest diameter in the plane of measurement to be recorded); minimum size: 10 mm on CT scan (CT scan thickness not greater than 5 mm); 10 mm on clinical examination; 20 mm on chest X-ray (if clearly defined). Malignant lymph nodes must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan thickness is recommended not to exceed 5 mm).

**Non-measurable disease—**all other lesions, including small lesions (longest diameter > 10 mm or pathological lymph nodes with short axis ≥ 10 mm and < 15 mm) and truly non-measurable lesions. Truly non-measurable lesions include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory disease of breast, lymphatic involvement of the skin or lung, mass in abdomen/abdominal organomegaly that cannot be measured by reproducible imaging techniques.

**Exceptions for measurable disease:** Including bone lesions, cystic lesions, and lesions previously treated locally. Bone scans, PET scans, or plain radiographs cannot be used to measure bone lesions, but they can be used to confirm whether bone lesions exist or have disappeared. If soft tissue components meet the above definition of measurability, soluble bone lesions or mixed soluble acute angle lesions with recognizable soft tissue components can be considered measurable lesions according to cross-sectional imaging techniques such as CT or MRI. If non-cystic lesions and cystic lesions coexist, non-cystic lesions are preferred as target lesions. Tumor lesions in previously irradiated areas or other locally regional treatment areas are usually not considered measurable lesions unless the lesions show progression.

All measurements should be recorded in metric notation using a ruler or caliper. All baseline evaluations should be performed as close as possible to the start of treatment and should be completed within 4 weeks before treatment.

**3 Measurement method**

The same assessment methods and the same technical description should be used to identify and report the same lesions during baseline and follow-up.

Clinical lesions are only considered measurable when they are superficial (e.g., nodule skin and palpable lymph nodes). For dermatosis lesions, it is recommended to estimate the size of the lesion area using color photographs (including a ruler).

CT and MRI are currently the best and most reproducible methods for measuring target lesions. Conventional CT and MRI use continuous layer thicknesses of ≤ 10 mm. Spiral CT uses 5 mm layer thickness for continuous reconstruction algorithms. This standard applies to thoracic, abdominal and pelvic tumors, while head and neck tumors and those of the extremities usually require special protocols.

Lesions seen on chest X-ray can be considered measurable if they are well defined and surrounded by aerated lung. CT is preferred.

When the primary endpoint of the trial is evaluation of objective response, ultrasonography (US) should not be used as the measurement method of tumor lesions. This method is not accepted in clinical practice. This method can be used as an alternative method to clinically measure superficial lymph nodes, subcutaneous lesions, and Thyroid nodule. US method can also be used to confirm the complete disappearance of superficial lesions that are usually evaluated by clinical examination.

**Tumor markers** alone cannot be used for response assessment. If the tumor marker is initially above the upper limit of normal, the marker must normalize when all tumor lesions disappear, and the subject can be considered to have a complete response. The elevated tumor marker must be accompanied by visible Disease progression to meet the requirements for progression of disease.

In a few cases, cytology and histology can be used to distinguish PR and CR (e.g., residual lesions in tumor type, such as Germ cell neoplasm, where known residual Benign neoplasm can be retained).

When effusion is known to be a potential adverse reaction of the therapy, a cytological confirmation of the neoplastic origin of any effusion present at the time of diagnosis or developing during therapy may be considered if the measurable tumor meets the response criteria or the criteria for stable disease to differentiate between response (or stable disease) and disease progression.

## 4 Tumor Response Evaluation

### 4.1 “Target” and “Non-target” Lesions Recorded at Baseline

All measurable lesions, a maximum of 2 lesions per organ and a maximum of 5 lesions overall, will be recorded and measured at baseline and represent all the organs as target lesions.

Target lesions should be selected according to size (lesions with the maximum diameter) and appropriateness so as to be accurately and repeatedly measured (through imaging technology or clinical method).

Sum of the longest diameters (LD) of all target lesions is calculated and reported as baseline sum of LD. Use the baseline sum of LD as the reference value for objective tumor description.

All other lesions (or sites of disease) should be recorded as non-target lesions and reported at baseline. These lesions do not need to be measured but should be recorded as present or absent throughout the follow-up.

### 4.2 Criteria for Response

**Criteria for Evaluation of Target Lesions**

| | |
|---|---|
| Complete response (CR): | All target lesions disappear. The short axis of any pathological lymph nodes (whether or not they are target lesions) must be reduced to <10 mm. |
| Partial response (PR): | Sum of diameters of target lesions is reduced by at least 30% as compared with the sum of diameters at baseline. |
| Disease progression (PD): | Sum of diameters of target lesions increases by at least 20% as compared to the smallest sum in the study (if the sum of diameters at baseline is the smallest sum in the study, it can be used as the reference). In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). |
| Stable disease (SD): | If the criteria for PR are not met and the criteria for PD are not met, the minimum sum of diameters at the time of study should be used as the reference. |

**Criteria for Evaluation of Non-Target Lesions**

| | |
|---|---|
| Complete response (CR): | Disappearance of all non-target lesions and normalization of tumor marker level. All lymph node sizes must be non-pathological (short axis < 10 mm). |
| Non-CR/SD: | Persistence of one or more non-target lesions and/or maintenance of higher level of tumor marker level than the normal limit. |
| Disease progression (PD): | Occurrence of one or more new lesions and/or clear progression of existing non-target lesions. |

***Although unequivocal progression of "non-target" lesions is an exception, reference should be made to the opinion of the treating physician and subsequent confirmation of progressive status.**

### 4.3Evaluation Criteria for Best Overall Response

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (the minimum measurements recorded from the start of treatment should be used as reference for PD). The best overall response of subjects is generally dependent on the completion of two measurements and confirmation criteria.

Patients who withdraw treatment due to overall deterioration in health status, and who do not have objective evidence of disease progression should be reported as having "symptomatic deterioration". Objective disease progression should be recorded whenever possible, even if treatment is withdrawn.

In some cases, it is difficult to distinguish normal tissue from residual lesions. When the assessment of complete response depends on this judgment, it is advisable to conduct research on residual lesions (fine needle aspiration/biopsy) to confirm the complete response status.

| Target lesions | Non-target lesions | New Lesion | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non- CR/Non- PD | No | PR |

| | | | |
|---|---|---|---|
| CR | Not evaluated | No | PR |
| PR | Not PD or not all evaluated | No | PR |
| SD | Not PD or not all evaluated | No | SD |
| Not fully evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

## 13.4 Appendix 4: Immune-Related Response Evaluation Criteria in Solid Tumour (iRECIST)

The following text is taken from the following reference: Lesley Seymour, Jan Bogaerts, Andrea Perrone, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017; 18: e143–52.

Assessment and Decision at RECIST 1.1 Progression

For participants with radiographic PD as determined by the Investigator per RECIST 1.1, the Investigator will decide whether to continue the participant on study treatment until repeat imaging results are obtained per participant management per iRECIST. This decision by the Investigator should be based on the overall clinical condition of the participant.

**Clinical stability is defined as follows:**

- Absence of clinical symptoms and signs indicating clinically significant disease progression.
- No decrease in ECOG performance status
- Intensification of treatment not required, including intensified pain relief, radiotherapy or other palliative therapy

Patients who are determined to be clinically unstable should discontinue study treatment from the first PD radiographic evidence as evaluated by the study site, and repeated imaging for confirmation of PD is not required.

If the investigator decides to continue treatment, the subject may continue to receive study treatment and tumor evaluation should be repeated every 4 to 8 weeks, and iRECIST should be used to confirm disease progression according to the investigator's assessment.

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For the purpose of iRECIST assessment, the first visit at which RECIST 1.1 disease progression is shown will be classified as a visit (overall) response of iUPD regardless of which factor causes disease progression. At this visit, the target and non-target lesions found at baseline according to RECIST 1.1 will be assessed as usual.

The new lesions will be classified as measurable or non-measurable using the same size threshold and rule as those used in the baseline lesion assessment according to RECIST 1.1. Up to 5 lesions (up to 2 lesions in each organ) from the measurable new lesions may be selected as new lesion-targets. The sum of diameters of these lesions will be calculated and differentiated from the sum of diameters of target lesions at baseline. All other new lesions will be classified as new lesion-non-target and subject to follow-up examination.

**Assessment at the time of confirmatory imaging**

In confirmatory imaging, participants will be classified as confirmed disease progression (overall response as iCPD) or show ongoing, unconfirmed progression (overall response as iUPD) or show stable or response (iSD / iPR / iCR).

**Confirmation of disease progression**

If any of the following conditions occur, the disease progression is considered to be confirmed, and the overall response is iCPD:

● Any factor constituting the basis of the initial iUPD shows deterioration.

For target lesions, deterioration refers to a further increase in the sum of diameters ≥ 5 mm compared to the previous time point of iUPD.

For non-target lesions, the deterioration is defined as any significant increase in the total lesions compared with the previous time point of iUPD; it is not required to meet the "clear" criteria of RECIST 1.1.

For new lesions, the deterioration indicates any of the following conditions:

- ✓ Increase in the sum of diameters of new lesions of ≥5 mm compared with the previous iUPD time point
- ✓ New non-target lesions with definite enlargement
- ✓ Occurrence of additional new lesions

● Any new factor that can make the assessment result of RECIST 1.1 be PD

***Persistent iUPD***

If any of the following conditions occur, the disease progression is not considered to be confirmed and the overall response remains iUPD:

- No evidence of disease progression mentioned above appears, and
- The sum of the diameters of the target lesions (initial target lesions) remains greater than the initial PD threshold (RECIST 1.1).

Additional imaging should be scheduled to confirm the presence of iUPD between 4 and 8 weeks after the imaging examination that identified iUPD. This may be equivalent to the next visit in the original visit schedule. Subsequent confirmatory imaging assessments proceed in the same way, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

***Recovery of iUPD***

If any of the following conditions occur, the disease progression is not considered as being confirmed, and the overall response is iSD/iPR/iCR:

- No evidence of disease progression mentioned above appears, and
- Sum of the diameters of target lesions (initial target lesions) is not greater than the initial PD threshold.

The response was classified as iSD or iPR (depending on the sum of the diameters of target lesions), or it was classified as iCR if all lesions resolved.

In this case, the initial iUPD is considered as pseudo-progression and the level of suspicion of progression is "reset". This means that, regardless of the specific time of the next visit showing radiological progression, it is reclassified as iUPD according to iRECIST and the response is reassessed as iCPD.

**Management after confirmatory imaging examinations**

If the repeat imaging examination fails to confirm PD according to iRECIST and the investigator's evaluation, and the participant's clinical condition continues to be stable, the study treatment can be continued and the examination should be conducted according to the regular imaging examination plan. If PD is confirmed, the participant will discontinue the study treatment.

Disease progression identified at the post-false progression rebound visit

Any of the following suggests iUPD after the disappearance of pseudo-progression (i.e., achieving iSD/iPR/iCR):

- target lesions

The sum of diameters reaches the PD threshold for the first time or after the first pseudo-progression disappears (increase ≥ 20% from the minimum and ≥ 5 mm). The minimum is always the minimum sum of diameters observed before or after the pseudo-progression event throughout the trial.

- nonevaluated non-target lesions

If non-target lesions have never shown unequivocal progression, the first unequivocal progression will cause iUPD.

If non-target lesions previously showed definite progression and the progression did not resolve, any further significant growth of non-target lesions (as a whole) would cause iUPD.

- new lesions

New lesion first appears

  - Additional new lesions develop

New lesions previously found show that the sum of diameters of new lesions increases by ≥5 mm from its minimum value

Non-target lesions previously found showing any significant growth

If any of the above events occur, the total response at the visit is iUPD, and the iUPD assessment process will be repeated (see the assessment at confirmatory imaging above). Disease progression must be confirmed prior to the occurrence of iCPD.

With the exception of one exception, the decision process is the same as the iUPD confirmation process for the initial PD, which is: if new lesions appear in the previous iUPD and the load of new lesions increases from its minimum value at the confirmatory imaging examination (for new lesions, the sum of diameters increases ≥ 5 mm from its minimum value), the iUPD cannot regress to iSD or iPR. Until the load of new lesions decreases to iSD or iPR, or until the confirmatory factors cause iCPD.

## 13.5 Appendix 5: Cardiac disorder defined by New York Heart Association

Grade I: The patient has heart disorder, but the daily activity is not limited, and general physical activity does not cause excessive fatigue, palpitations, dyspnea or angina pectoris.

Grade II: Slight physical activity is mildly restricted in patients with heart disorder. No conscious symptoms at rest, but excessive fatigue, palpitations, dyspnea or angina pectoris during general physical activity.

Grade III: The patient has heart disorder, resulting in a significant limitation of physical activity. Asymptomatic at rest, but over-fatigue, palpitation, dyspnea or angina pectoris can be induced by less than general physical activity.

Grade IV: Heart disorder patients cannot perform any physical activity, and heart failure symptoms occur even at rest, which worsen after physical activity.

### 13.6 Precautions for allergic reactions

**Required equipment**

- Tourniquet
- Oxygen
- Epinephrine used subcutaneously, intravenously and/or endotracheally according to standard care
- Antihistamines
- Corticosteroids
- Intravenous fluids, infusion tube, catheter, and tape

**Operation**

In the case of suspected allergic reactions during study drug infusion, the following procedures should be implemented:

1. Discontinue study drug infusion;
2. Use a tourniquet near the injection site to slow systemic absorption of the study drug. Do not occlude arterial blood flow in the affected limb;
3. Maintain airway patency;
4. Administer antihistamines, Epinephrine, or other medications as directed by the on-duty physician according to the patient's condition;
5. The patient is observed and the observation results are recorded.

## 13.7 Appendix 7 Pre-existing autoimmune diseases

The history of acquired or congenital immunodeficiency or autoimmune disease should be carefully enquired. Patients with a history of the immunodeficiency or autoimmune disease shown in the table below were excluded from the study. The possible exception to this exclusion criterion was the patient with such history as e.g. dyscrasia or childhood arthralgia, in which case the clinical suspicion of autoimmune disease was less likely. Patients with a history of autoimmune-related thyroid function decreased on a stable dose of thyroid replacement hormone were eligible for this study. In addition, the transient autoimmune manifestations (e.g. acute Lyme arthritis) after treatment with an anti-infection drug were not excluded. In case of any uncertainty on the exclusion criterion of autoimmune disease, please contact the medical monitor.

**Autoimmune Diseases and Immunodeficiency**

| | | |
|---|---|---|
| Acute disseminated encephalomyelitis | acquired Epidermolysis bullosa | Ord Thyroiditis |
| Addison’s disease | Pemphigoid gestationis | Pemphigus |
| Ankylosing spondylitis | Giant cell arteritis | Pernicious anaemia |
| Antiphospholipid antibodies syndrome | Goodpasture syndrome | Polyarteritis nodosa |
| Aplastic anaemia | Graves disease | Arthritis |
| Autoimmune haemolytic anaemia | Guillain-Barre syndrome | Polyglandular Autoimmune Syndrome |
| Autoimmune hepatitis | Hashimoto’s thyroiditis | Biliary cirrhosis primary |
| Autoimmune hypoparathyroidism | IgA nephropathy | Psoriasis |
| Autoimmune hypophysitis | Inflammatory Bowel Disease | Reiter syndrome |
| Autoimmune myocarditis | Cystitis interstitial | R Arthritis |
| Autoimmune oophoritis | Kawasaki disease | Sarcoidosis |
| Autoimmune orchitis | Lambert-Eaton Myasthenic syndrome | Scleroderma |
| Autoimmune thrombocytopenic purpura | Lupus erythematosus | Sjögren's syndrome |
| Behcet's disease | Lyme disease – Chronic | Stiff-Person syndrome |
| Bullous pemphigoid | Meniere’s syndrome | giant Arteritis |
| Chronic fatigue syndrome | Mooren ulcer | Colitis ulcerative |
| Chronic Inflammatory Demyelinating Neuropathy | Circumscribed scleroderma | Vitiligo |
| | Multiple sclerosis | Vogt-Koyanagi-Harada syndrome |
| Chung-Strauss syndrome | Myasthenia gravis | Wegener's granulomatosis |
| Crohn’s Disease | Neuromyotonia | |
| Dermatomyositis | Opsoclonus myoclonus Syndrome | |
| Type 1 Diabetes mellitus | Optic neuritis | |
| Familial dysautonomia | | |

## 13.8 Appendix 8: Summary of changes

**Protocol 4.0: September 13, 2024**

| Section number and title | Previous Text | Description after change | Brief Rationale |
|---|---|---|---|
| 1.1 Abstract<br>Inclusion Criteria<br>5.1 Inclusion Criteria | 3. Recurrent or metastatic Squamous cell carcinoma of head and neck, including the oral cavity, oropharynx, hypopharynx, larynx, or paranasal sinuses, that is no longer suitable for local treatments such as surgery or radiation therapy. | 3. Histologically or cytologically confirmed advanced, recurrent, or metastatic head and neck squamous cell carcinoma originating in the oral cavity, oropharynx, hypopharynx, larynx, or paranasal sinuses, not amenable to local treatments such as surgery or radiotherapy; | Adjust the wording to avoid ambiguity. |
| 1.1 Summary<br>Overall Design<br>Phase II study<br>Duration of Interventation<br>4.1 Overall Design<br>4.3 Phase II study<br>6.2.3 Dose sequence and duration of administration | until the investigator determines that the patient has had a RECIST 1.1 radiographic disease progression, intolerable toxicity, or has requested to discontinue the study treatment or withdraws consent to remain in the study, or the investigator determines that the patient needs treatment withdrawal, or the treatment time with JS001 has reached a maximum of 2 years (whichever occurs first). | until disease progression by radiological criteria according to RECIST 1.1, intolerable toxicity, patient request to discontinue study treatment or withdraw informed consent, or investigator's judgment that treatment withdrawal is necessary, or up to 2 years of treatment (whichever occurs first). | Specify the maximum study treatment duration. |
| 4.4 End of Study | None | The end of study is defined as 18 months after the enrollment of the last subject. | Specify the end of study time. |

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