Clinical Study Protocol

Protocol Title:	**A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Compare Toripalimab (JS001) Combined with Standard Chemotherapy vs Placebo Combined with Standard Chemotherapy in the Treatment of Advanced or Metastatic Esophageal Squamous Cell Carcinoma without Previous Systemic Chemotherapy**
Protocol Number:	**JS001-021-III-ESCC**
Medicinal Product(s):	**Toripalimab (JS001)**
Study Phase:	**Phase 3**
Sponsor:	**Shanghai Junshi Biosciences Co., Ltd. Floor 13, Building 2, Haiqu Road No. 36 and 58, Free Trade Zone, Shanghai, China, 200120**
Medical Monitor:	**Xusheng Ren, Medical Manager**
Principal Investigator:	**Prof. Ruihua Xu**
Protocol Number:	**4.0**
Protocol Date:	**June 30, 2020**
Previous Versions:	**v1.0, October 25, 2018** **v2.0, April 30, 2019** **v3.0, August 19, 2019**

Table of Contents

List of Tables

List of Figures

Sponsor's Statement

Protocol Title:	A Phase 3, randomized, double-blind, placebo-controlled, multi-center study to compare toripalimab (JS001) combined with standard chemotherapy vs placebo combined with standard chemotherapy in the treatment of advanced or metastatic esophageal squamous cell carcinoma without previous systemic chemotherapy
Protocol Number:	JS001-021-III-ESCC
Version Number and Version Date:	Version 4.0, June 30, 2020

I will conscientiously fulfill the Sponsor's obligations according to China's Good Clinical Practice (GCP) regulations and be responsible for initiating, conducting, organizing, funding, and monitoring this clinical study. I will, in accordance with the relevant national laws and regulations, provide active treatments to patients with serious treatment-emergent adverse events during the clinical study and cover the corresponding cost of treatment and will also provide rational economic compensation for the damage caused by the serious adverse reaction that is determined to be related to the study drug. I agree to conduct the clinical study in accordance with the design and provisions in this protocol.

Sponsor: Shanghai Junshi Biosciences Co., Ltd.

Name of Project Lead: Wei Liu

Title: Head of the Department of Medical Sciences

Project Lead (signature):_____ Date:____dd____mm____yyyy

Investigator's Statement

I have read the clinical study protocol (version number: 4.0, dated June 30, 2020), entitled "A Phase 3, randomized, double-blind, placebo-controlled, multi-center study to compare Toripalimab (JS001) combined with standard chemotherapy vs placebo combined with standard chemotherapy in treatment of advanced or metastatic esophageal squamous cell carcinoma without previous systemic chemotherapy," and agree to conduct this clinical study in accordance with the study protocol, the current laws and regulations, and the ethical principle in the Declaration of Helsinki.

I agree to comply with the guidelines of GCP and other applicable National Medical Products Administration (NMPA) regulations/guidelines on the quality management rules for drug clinical studies.

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

Principal investigator name: _____

Signature:_____ Date:____dd____mm____yyyy

Protocol Synopsis

Study Title:	**A Phase 3, randomized, double-blind, placebo-controlled, multi-center study to compare toripalimab (JS001) combined with standard chemotherapy vs placebo combined with standard chemotherapy in the treatment of advanced or metastatic esophageal squamous cell carcinoma without previous systemic chemotherapy**
Protocol Number:	JS001-021-III-ESCC
Version Number:	4.0
Study Medication:	Toripalimab (JS001)
Study Phase	Phase 3
Indications:	Advanced or metastatic esophageal squamous cell carcinoma
Sponsor:	Shanghai Junshi Biosciences Co., Ltd.

Objectives and endpoints

This study is intended to evaluate the efficacy and safety of toripalimab in combination with paclitaxel and cisplatin (hereafter referred to as TP regimen) vs placebo in combination with TP regimen in patients with advanced or metastatic esophageal squamous cell carcinoma (ESCC) who have not received systemic chemotherapy previously. The objectives of this study are summarized as follows.

Study objectives	Corresponding endpoints
Primary efficacy objective:	
1) To evaluate the differences in PFS (as assessed by the BICR per RECIST 1.1 criteria) and OS following toripalimab in combination with TP regimen compared to placebo in combination with TP regimen in all randomized patient populations with advanced or metastatic ESCC who had not previously received systemic chemotherapy	• PFS is defined as the time from randomization to the first progression of disease, or the time from randomization to death for any reason, whichever comes first, will be determined by the BICR in accordance with RECIST 1.1criteria. • OS is defined as the time from randomization to death for any cause.

Study objectives	Corresponding endpoints
Secondary efficacy objectives:	
2) To evaluate the differences between arms in ORR, DCR, DOR, and TTR by the investigator and by the BICR in accordance with RECIST v1.1 3) To evaluate the differences between arms in PFS by the investigator in accordance with RECIST v1.1, 4) To evaluate the differences between arms in ORR, DCR, DOR, and TTR by the investigator in accordance with irRECIST 5) To evaluate the 1- and 2-year PFS rates between treatment arms 6) To evaluate the 1- and 2-year OS rates between treatment arms 7) To evaluate the quality of life (QoL) following toripalimab in combination with TP regimen compared to placebo in combination with TP regimen in all randomized population	• ORR is defined as the proportion of patients with the best overall response of CR or PR • DOR is defined as the time from first documented response to first documented evidence of disease progression or death, whichever comes first. • DCR is defined as the proportion of patients with the best efficacy of CR, PR, or SD. • TTR is defined as the time from randomization to the first documentation of objective response (CR or PR). • 1 year and 2 years PFS rates are defined as the proportion of patients who are alive and have no documented progression of disease 1 year and 2 years after randomization, as evaluated in accordance with RECIST 1.1 criteria. • OS rate at 1 year and 2 years, defined as the proportion of patients who are alive 1 year and 2 years after randomization. • PRO analyzed as mean change from baseline, by cycle, in EORTC QLQ-C30 and QLQ-OES18 score
Safety objective:	
8) To evaluate the safety and tolerability of toripalimab in combination with TP regimen compared to placebo in combination with TP regimen	• Safety and tolerability characterized by incidence and severity of AE and SAE, where severity is determined in accordance with CTCAE 5.0
Exploratory objectives:	
9) To evaluate predictive or prognostic biomarkers (tissue and/or plasma) related to the status of disease activity and response to treatment 10) To identify the possible mechanism of the drug resistance to the study treatment through comparative analysis of the potential biomarkers in biopsy tissue samples and blood samples prior to treatment and after progression of disease	• Correlation between biomarkers in archival or fresh tissue specimen and blood (including but not limited to PBMC, PD-L1, MSI, 11q13, tumor mutation burden, and other) and disease status, mechanism of drug resistance, and/or response to toripalimab. • The incidence and titer of ADA of toripalimab and potential correlation between the immunogenicity response and pharmacokinetics, safety, and efficacy • The feasibility of biopsy of sites with obvious increase of tumor volume to differentiate between the immunoregulatory effects of toripalimab (i.e., pseudoprogression/ tumor immune infiltration) and true progression of disease.

AE = adverse event; ADA = anti-drug antibody; BICR = blinded independent central review; CR = complete response; CTCAE = common terminology criteria for adverse event; DCR = disease control rate; DOR = duration of response; EORTC = European Organisation for research and treatment of cancer; QLQ-C3 = quality of life instruments for cancer patients; ESCC = esophageal squamous cell carcinoma; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; MSI = microsatellite instability; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death receptor – ligand 1; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; PRO = patient-reported outcome; QLQ-OES18 = supplementary scale for esophageal cancer patients; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; TTR = time to response.

Study design

Description of the study

This is a Phase 3 randomized, double-blind, multi-center, placebo-controlled study. The objective of this study is to compare the efficacy and safety of toripalimab in combination with the TP regimen and placebo in combination with the TP regimen in patients with advanced or metastatic ESCC who have not received systemic chemotherapy previously.

Eligible patients will be randomized (1:1) into Group A (toripalimab combined with TP regimen) or Group B (placebo combined with TP regimen). The stratification factors include Eastern Cooperative Oncology Group (ECOG) performance status score (0 or 1) (see Appendix 9) and previous radiotherapy (yes or no). The treatment plan will include an induction period and a maintenance period in the study as follows:

- Toripalimab/placebo dosing (induction period): 240 mg intravenously, once every three weeks on Day 1 of each 3-week cycle, in combination with TP, for a maximum of 6 cycles.
- Toripalimab/placebo dosing (maintenance period): 240 mg intravenously, once every three weeks, on Day 1 of each 3-week cycle

Treatment group	**Induction period (3 weeks/cycle for up to 6 cycles, dosing on Day 1 of each cycle)**	**Maintenance period (3 weeks/cycle, dosing on Day 1 of each cycle)**
Group A	Toripalimab (240 mg) and paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2)	Toripalimab (240 mg)
Group B	Placebo and paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2)	Placebo

Study treatment will continue until intolerable toxicity, PD, patient refusal to continue study drug treatment, judgment by investigator that the patient needs to be withdrawn from the

treatment, or up to two years of treatment, whichever occurs first. During the induction period, if one or both chemotherapeutic agent is discontinued due to toxicity, the study drug is continued until criteria for discontinuation of treatment are met. For patients with progression of disease (PD) in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; the patient may continue to receive the study drug in blinded state after the investigator determines, and the Sponsor agrees, that the patient may benefit from continuation of study drug and after the patient signs the corresponding informed consent form (ICF) for continuation of treatment after disease progression.

Planned number of patients

It is planned to enroll approximately 500 patients with advanced or metastatic ESCC who have not previously received systemic chemotherapy for ESCC. They will be randomized at a 1:1 ratio into the toripalimab in combination with the TP regimen group or the placebo in combination with the TP regimen group (i.e., 250 patients each in groups A and B).

Target population

Inclusion criteria

For inclusion in the study, patients must fulfill all the following:

1. Inclusion criteria for esophageal cancer

    a) Histologically or cytologically confirmed locally advanced/recurrent or metastatic ESCC that is not suitable for curative resection;

    b) No prior systemic antitumor therapy for recurrent or metastatic tumor;

    c) No relapse in an interval of at least 6 months after the end of the last dose in the patients previously receiving adjuvant, neoadjuvant chemotherapy/radiotherapy/ chemoradiotherapy, and radical therapy for non-metastatic disease (no relapse in an interval of at least 12 months after the end of the last dose in the patients previously receiving adjuvant chemotherapy/chemoradiotherapy with TP regimen);

    d) No risk of major hemorrhage or esophageal fistula, for example, a large ulcer at the lesion is considered a risk for major hemorrhage and esophageal fistula, so the patient would not be suitable for enrollment. The risk for hemorrhage or fistula should be carefully evaluated for patients with direct invasion to adjacent organs,

e.g., aorta or trachea (T4b disease), prior to enrollment, and the Sponsor should be consulted prior to enrollment.

2. General criteria for inclusion:

   a) Signed ICF;

   b) Male or female between 18 to 75 years old;

   c) ECOG performance status score of 0 or 1;

   d) Expected survival longer than 3 months;

   e) Agreement upon providing archival tumor tissue specimen or fresh tumor biopsy for biomarker analysis;

   f) At least 1 measurable lesion in accordance with RECIST 1.1. If a lesion was previously irradiated and confirmed PD has occurred at this site, then this lesion can be used as a measurable lesion;

   g) Adequate organ function as defined below:

      Hematology: neutrophil $\geq 1.5\times10^9$/L, hemoglobin ≥9 g/dL and platelet $\geq 100\times10^9$/L;

      Hepatic function: bilirubin ≤1.5× upper limit of normal (ULN) (patients who are known to have Gilbert's syndrome's and a serum bilirubin level ≤3× ULN can be enrolled), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5× ULN (in case of hepatic metastasis, AST/ALT≤5× ULN), and alkaline phosphatase (ALP) ≤3× ULN (in case of hepatic or bone metastasis, ALP≤5× ULN); albumin ≥3 g/dL;

      International normalized ratio or prothrombin time or activated partial thromboplastin time ≤1.5× ULN;

      Renal function: serum creatinine ≤1.5× ULN or estimated glomerular filtration rate in accordance with Cockcroft-Gault formula: creatinine clearance ≥60 mL/min

$$\frac{(140 - \text{age})\text{x}(\text{weight，kg})\text{x}(0.85，\text{for women})}{72\ \text{x}(\text{serum creatinine，mg/dL})}$$

      or:

$$\frac{(140 - \text{age})\text{x}(\text{weight，kg})\text{x}(0.85，\text{for women})}{0.818\,\text{x}(\text{serum creatinine，}\mu\text{mol/L})}$$

h) Female patients who meet the following criteria are eligible:

Female patients with no childbearing potential (e.g., physiologically infertile) defined as meeting any one of the following conditions:

- Hysterectomy performed;
- Bilateral oophorectomy (oophorectomy) performed;
- Bilateral tubal ligation performed; or
- Postmenopausal (total duration of menopause ≥1 year).

Female patients with childbearing potential who have a negative serum pregnancy test result at screening (within 7 days prior to the first dose of study drug) and to initiate adequate contraceptive measure during screening and continue throughout the study until 60 days after the last dose of the study drug. Adequate contraceptive measures taken continuously, according to the instruction on the contraceptive product and physician's guidance, are defined as follows:

- Any intrauterine device confirmed to have a failure rate for contraception lower than 1% per year;
- Dual-barrier contraception, defined as a condom with spermicidal gel, foam, suppository, or film; a diaphragm with spermicide; or a male condom used in addition to a diaphragm.

Exclusion criteria

Patients who fulfill any of the following criteria are not eligible for this study:

1. Cancer-specific exclusion criteria:

a) Active or untreated central nervous system metastasis (e.g., brain or leptomeningeal metastasis) confirmed by computerized tomography (CT) or magnetic resonance imaging at screening and previous radiological evaluation. Patients who previously received treatment of brain or leptomeningeal metastasis, stabilized for ≥2 months

and discontinued systemic hormone therapy (>10 mg/day of prednisone or equivalent) for >28 days prior to randomization may participate in the study;

b) Uncontrolled tumor-related pain;

c) Uncontrolled pleural effusion, pericardial effusion, or ascites requiring repeated drainage (once per month or more frequently). Indwelling catheter (e.g., PleurX®) is allowed;

d) Uncontrollable or symptomatic hypercalcemia (ionized calcium >1.5 mmol/L or calcium >12 mg/dL or corrected serum calcium > ULN);

e) History of malignant tumors, except for esophageal cancer, within 5 years prior to randomization. However, patients with malignant tumors that have a negligible risk of metastasis or resulting in death (e.g., an expected 5-year survival rate > 90%) and are expected to be cured after treatment can be enrolled, for example, cervical carcinoma in situ, basal or squamous cell skin cancer, localized prostate cancer, or ductal carcinoma in situ treated by curative resection.

f) Palliative radiotherapy within 28 days prior to enrollment or radiopharmaceutical therapy within 8 weeks prior to enrollment, except for localized, palliative radiotherapy for metastatic bone lesions. Localized, palliative radiotherapy of a symptomatic lesion (such as bone metastasis or cancer invasion of nerves) must be completed prior to enrollment and the patient must have recovered from the side effects of such palliative radiotherapy prior to enrollment. There is no minimum requirement for the period of time from recovery to enrollment/randomization.

g) Patients with bone metastasis of multiple vertebra that are prone to fractures and puts the patient at risk of paraplegia, except patients who are assessed by a specialist as stable and not in need of treatment;

h) Patients with advanced cancer with metastasis to vital organs and who are at risk of developing life-threatening complications in the short term (e.g., liver metastases involving >50% of total liver volume);

i) Patients with known complete esophageal obstruction per endoscopy who have undergone necessary tracheal or esophageal stenting;

j) Patients who have a body mass index of <17.5, weight loss of >10% within 2 months prior to the first dose of study treatment (excluding weight loss attributed to drainage of massive pleural effusion or ascites), or other manifestations of severe malnutrition.

2. General medical exclusion criteria:

a) Female patients who are pregnant, lactating, or plan to become pregnant during the study;

b) History of severe allergic, anaphylaxis, or other hypersensitivity reaction to a chimeric or humanized antibody or fusion protein;

c) Known allergy or hypersensitivity to the biological products manufactured from Chinese hamster ovary cells or any component of toripalimab drug product;

d) History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid syndrome-related vascular thrombosis, Wegener's granulomatosis, Sjogren's syndrome, Guillain-Barre syndrome, multiple sclerosis, vasculitis, and glomerulonephritis (see Appendix 11 Listing of Autoimmune or Immunodeficiency Disorders to be Considered During Screening);

- Patients with hypothyroidism who are on stable-dose thyroid hormone replacement therapy can be enrolled in this study (refer to Appendix 6 for the replacement therapy for hypothyroidism);
- Patients with type I diabetes whose blood glucose is controlled through stable-dose insulin can be enrolled in this study;
- Patients with eczema, psoriasis, chronic lichen simplex, or vitiligo with cutaneous manifestations only (e.g., patients with psoriatic arthritis will be excluded from the study) are allowed to be enrolled in this study if they meet the following conditions:
  - Rash must be <10% of body surface area;
  - The disease has been fully controlled at baseline, and only low-potency topical steroid therapy is needed;

- No acute exacerbation of underlying diseases in the past 12 months (no need for psoralen plus ultraviolet A radiation (PUVA), methotrexate, retinol, biological preparation, oral calcineurin inhibitor, or high-potency systemic steroid therapy).

e) History of idiopathic pulmonary fibrosis, organized pneumonia (e.g., obliterative bronchiolitis), drug-induced pneumonia, idiopathic pneumonia, interstitial pneumonia, or evidence of active pneumonia found during chest CT screening scan;

f) Patients with a positive test result of human immunodeficiency virus;

g) Patients with hepatitis B virus (HBV) (known positive HBV surface antigen hepatitis B surface antigen [HBsAg] and HBV deoxyribonucleic acid [DNA] ≥1000 cps/mL or 200 IU/mL or ≥ULN at each study site) or hepatitis C virus (HCV):

- Patients with a previous HBV infection will be eligible to participate in this study only when their HBV DNA is negative (HBV DNA <1000 cps/mL or 200 IU/mL or <ULN) in a required HBV DNA test;
- Patients with a positive HCV antibody can participate in this study only if they have negative HCV ribonucleic acid (RNA) by polymerase chain reaction.

h) Patients with active pulmonary tuberculosis (clinical diagnosis includes clinical history, physical examination, and radiological findings, as well as the tuberculosis test performed in accordance with local medical procedures);

i) Serious infection within 28 days prior to randomization, including but not limited to the infection complications, bacteremia, and severe pneumonia requiring hospitalization;

j) Treatment with oral or intravenous (iv) antibiotics within 2 weeks prior to randomization; patients receiving preventive antibiotic therapy (e.g., for prevention of urinary tract infection or prevention of exacerbation of chronic obstructive pulmonary disease) can be enrolled;

k) Serious cardiovascular diseases, e.g., heart disease defined by New York Heart Association (Grade 2 or above), myocardial infarction within 3 months prior to randomization, unstable arrhythmia, unstable angina pectoris, cerebrovascular accident, or transient cerebral ischemic attack. Patients with known coronary artery

disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must receive the treatment considered by the attending physician as the optimal treatment and may consult a cardiologist when necessary;

l) Major surgery (except for diagnostic operation) within 28 days prior to randomization or expected major surgery during the study;

m) Previous allogeneic bone marrow transplantation or solid organ transplantation.

n) Use of attenuated live vaccine within 28 days prior to randomization or plan to use such attenuated live vaccine during the study;

o) Any other disease, metabolic disorder, physical examination finding, or abnormal laboratory examination that will possibly lead to contraindicated use of the study drug affect the interpretation of the study results, or place the patient at high risk of treatment-related complications of diseases or conditions;

3. Exclusion criteria related to medications:

a) Patients who have previously received any approved anticancer traditional Chinese medicine within 2 weeks prior to the first dose of study drug;

b) Patients who have used other investigational products or participated in other clinical studies for therapeutic objectives within 28 days prior to randomization (including signing an ICF for other trials and failure of screening);

c) Previous immune checkpoint blocking therapy, for example, therapeutic antibodies of anti-programmed death receptor-1 and anti-PD-antibody;

d) Previous systemic immunomodulator therapy, including but not limited to interferon or interleukin-2, within 2 weeks or 5 half-lives prior to randomization, whichever lasts longer. Previous vaccinations with cancer vaccines are allowed;

e) Use of systemic immunosuppressive drugs within 2 weeks prior to randomization, including but not limited to prednisone (>10 mg/day prednisone or equivalent), cyclophosphamide, azathioprine, methotrexate, thalidomide, and tumor necrosis factor;

- Patients who have received a short-term, low-dose, systemic immunosuppressant (e.g., a single dose of dexamethasone for nausea) can participate

in this study after discussion between investigators and the medical monitor and approval by the medical monitor;

- Patients who use inhaled corticosteroids for treatment of chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for treatment of orthostatic hypotension, and low-dose glucocorticoids (≤10 mg/day prednisone or equivalent drug) supplement for treatment of hypoadrenocorticism are eligible.

f) Patients who have previously received the hematopoietic growth factors (e.g., granulocyte colony-stimulating factor and erythropoietin) or blood transfusion within 2 weeks prior to randomization.

4. Exclusion criteria related to chemotherapy:

a) History of allergy to cisplatin, carboplatin, or other platinum-based compounds;

b) Grade 2 or higher peripheral neuropathy according to the Common Terminology Criteria for Adverse Events v5.0.

The end of the study and duration of the study

The end of the study is defined as the date when approximately 366 deaths required for the primary analysis of overall survival (OS) in the intent-to-treat (ITT) population have been observed. The duration of the study is estimated to be approximately 39 months from the first patient signing the ICF to the end of this study.

Study drug and administration

Toripalimab, placebo, and chemotherapeutic agents will be provided by the Sponsor.

Group A: Toripalimab in combination with TP regimen

Group B: placebo in combination with TP regimen

Toripalimab/placebo dosing (induction period): 240 mg iv infusion, day 1, once every three 3 weeks (Q3W).

Toripalimab/placebo dosing (maintenance period): 240 mg iv infusion, day 1, Q3W.

Paclitaxel: 175 mg/m^2 iv infusion over 3 hours or per local clinical practice, day 1, Q3W, for up to 6 cycles.

In order to prevent allergic reactions, 20 mg dexamethasone can be administered orally 12 and 6 hours and 50 mg diphenhydramine (or similar product) and an H2 receptor antagonist (cimetidine 300 mg or ranitidine 50 mg) can be used within 1 hour prior to paclitaxel. The prophylactic premedication for paclitaxel may be adjusted according to the standard practice of the site.

Cisplatin: 75 mg/m^2 diluted with 500 mL 0.9% sodium chloride administered as an iv infusion at a rate of approximately 1 mg/min or per local clinical practice on Day 1 of each 3-week treatment cycle for up to 6 cycles.

It is recommended that the patients be adequately hydrated prior to and for up to 24 hours after cisplatin administration. Adequate hydration can be achieved by 500-1000 mL 0.9% sodium chloride solution via iv infusion prior to cisplatin administration and then 1000-2000 mL after administration. Mannitol and furosemide (Lasix) can be administered before and after hydration to ensure a urine volume of 2000～3000 mL per day. Attention should be paid to fluid and electrolyte balance. Procedures to ensure adequate hydration may be adjusted according to the standard practice of the research site.

During induction period, toripalimab will be administered prior to paclitaxel and cisplatin on Day 1 of each cycle.

When the induction period is completed, toripalimab/placebo will be administered during the maintenance period until intolerable toxicity, PD, patient refusal to continue study drug treatment, judgment by investigator that the patient needs to be withdrawn from the treatment, or up to two years of treatment, whichever occurs first.

Statistical methods

Determination of sample size

Approximately 500 patients with advanced or metastatic ESCC who have not received previous systemic chemotherapy for ESCC will be enrolled in this study and randomized (1:1) into the toripalimab in combination with TP group (Group A) and placebo in combination with TP group (Group B) (i.e., 250 patients each in group).

The sample size was calculated based on the dual primary efficacy endpoints of progression-free survival (PFS), as evaluated by the blinded independent central review (BICR) per RECIST 1.1, and OS. A hierarchical testing will be used for PFS and OS analysis

at an overall significance level of 2-sided 0.05, i.e., the overall α level (2-sided 0.05) will be firstly used for the hypothesis test of PFS; if the null hypothesis of PFS is rejected, the hypothesis test of OS will be performed at the two-sided significance level of 0.05.

For PFS, 283 PFS events are expected to be observed in approximately 500 patients enrolled approximately 24 months after randomization of the first patient. This will provide 85% statistical power to detect an improvement in PFS for toripalimab in combination with the TP regimen vs placebo in combination with the TP regimen in patients with advanced or metastatic ESCC who have not previously received systemic chemotherapy at the two-sided significance level of 0.05 to detect a corresponding hazard ratio (HR) of 0.7.

For OS, 366 OS events are expected to be observed in approximately 500 patients enrolled approximately 39 months after randomization of the first patient, thereby there is 85% statistical power to detect an improved OS for toripalimab in combination with the TP regimen vs placebo in combination with the TP regimen in patients with advanced or metastatic ESCC who have not previously received systemic chemotherapy at the two-sided significance level of 0.05 to detect a corresponding HR of 0.73. One planned interim analysis of OS will be performed at the time of the PFS analysis (approximately 24 months after randomization of the first patient).

Efficacy analysis

Primary efficacy outcome

The primary efficacy endpoints of the study are PFS (as evaluated by BICR per RECIST 1.1) and OS. The hierarchical testing will be used for PFS and OS analysis at the overall significance level of 2-sided 0.05. That is, all α levels (2-sided 0.05) will be firstly used for the hypothesis test of PFS; if the null hypothesis of PFS is rejected, the hypothesis test of OS will be performed at the two-sided significance level of 0.05.

PFS per RECIST v1.1 is defined as the time from randomization to first recorded PD or to death for any cause, whichever is earlier. Patients without PD or death will be censored on the day of the last complete tumor evaluation. Patients who have not received any tumor evaluation during the study and are not dead will be censored 1 day after randomization. Patients who do not report any PD nor start any anticancer therapy unspecified in the protocol will be censored on the day of the last evaluable tumor evaluation prior to the start of subsequent anticancer therapy. The stratified log-rank test will be used for PFS analysis,

stratification factors include ECOG performance status score (0 or 1) and previous radiotherapy (yes or no). The Kaplan-Meier (KM) method will be used to estimate the median PFS in each treatment group; the 95% confidence interval (CI) of median PFS will be estimated through the Brookmeyer-Crowley method using log-log function conversion to reach normal approximation. The HR of PFS and its 95% CI will be estimated using the stratified Cox proportional hazard model.

OS is defined as the time from randomization to death for any cause. Patients without death recorded will be censored on the last known survival date. Patients without any follow-up information will be censored on the day after randomization. The same analytical method for PFS will be used for analysis of OS.

Secondary efficacy outcome

The secondary efficacy endpoints include ORR, disease control rate (DCR), duration of response (DOR), and time to response (TTR) evaluated by BICR and by investigators in accordance with RECIST 1.1, PFS evaluated by investigators in accordance with RECIST 1.1, PFS, ORR, DCR, DOR, and TTR evaluated by investigators in accordance with Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST), as well as the PFS and OS rates at 1 year and 2 years. The specific definitions for these endpoints are as follows:

- The PFS rate at 1 year or 2 years is defined as the percentage of patients who are alive and have no documentation of PD or death within 1 year or 2 years after randomization.
- The OS rate at 1 year and 2 years is defined as the percentage of patients who are alive within 1 year or 2 years after randomization.
- The objective response rate (ORR) is defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR).
- DCR is defined as the proportion of patients with a best overall response of CR, PR, or stable disease (SD).
- DOR is defined as the time from the first recorded response (CR or PR) to the first recorded occurrence of disease progression or death, whichever is earlier. DOR is analyzed only for patients with a best overall response of CR or PR. Patients without disease progression or death after achieving response will be censored on the date of the

last tumor evaluation. If no tumor evaluation is performed after achieving response, patients will be censored 1 day after the tumor evaluation documenting response.

- TTR is defined as the time from randomization to first recorded response (CR or PR). TTR will be calculated only for patients with a best overall response of CR or PR, without censoring.

The KM method used for the primary efficacy dual endpoints of PFS and OS will be used for the secondary efficacy endpoints of DOR and TTR. The percentage of patients in each treatment group will be calculated for ORR and DCR. The Clopper-Pearson method will be used to calculate their 95% CIs; the 95% CI for the difference in the percentage between groups will be estimated using the Newcombe method. The KM method will be used to estimate the PFS and OS rates at 1 year and 2 years in each treatment group. The 95% CI will be estimated using the Greenwood formula, and the 95% CI for the intergroup difference in PFS and OS rate will be estimated using the Newcombe method.

Interim analysis

One interim analysis of OS is planned in this study.

The interim analysis of OS is planned to be conducted at the time of the definitive PFS analysis, i.e., when approximately 283 PFS events and 212 OS events have occurred, which is expected approximately 24 months after the first patient is randomized. However, the exact time of this interim OS analysis will depend on the actual time when the number of required events for the PFS analysis is reached.

The interim analysis will be performed by an independent statistical analysis service provider; the result of the interim analysis will be reviewed by independent data monitoring committee (IDMC), and advice will be provided to the Sponsor thereafter.

Independent data monitoring committee

An IDMC will be established to assess the safety, efficacy, and risk/benefit data from the study. The IDMC will include at least 2 clinicians and 1 biostatistician with professional knowledge of oncological trials. Prior to the final analysis of PFS, risk/benefit assessments will be conducted at regular data review meetings to ensure the safety of the patients. If any interim analysis is planned, the IDMC will also review the efficacy data. After review of the data, the IDMC will provide advice on continuation of the study, amendment to the protocol

or discontinuation of the study. The final decision will be made by the Sponsor. The procedures on management of the IDMC will be specified in a separate IDMC charter.

List of Abbreviations and Definition of Terms

Abbreviations	Definitions
AE	Adverse event
AESI	Adverse event of special interest
aPTT	Activated partial thromboplastin time
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ADA	Anti-drug antibody
BICR	Blinded independent central review
BSA	Body surface area
CCND1	Cyclin D 1
CI	Confidence interval
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CR	Complete response
CrCL	Creatinine clearance
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
EBV	Epstein-Barr virus
EC	Ethics 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
ESCC	Esophageal squamous cell carcinoma
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor

Abbreviations	Definitions
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER-2	Human epidermal growth factor receptor-2
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IFN	Interferon
IMP	Investigational drug
INR	International normalized ratio
irAE	Immune-related adverse events
IRC	Independent Review Committee
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent to treat
iv	intravenous(ly)
IxRS	Interactive voice/web response system
KM	Kaplan-Meier
MSI	Microsatellite instability
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NSG	NOD scid gamma
NIMP	Non-investigational medicinal drugs
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progression of disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand-1
PD-L2	Programmed death ligand-2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response

Abbreviations	Definitions
PRO	Patient-reported outcome
PT	Preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QLQ-C30	Quality of Life - Core Questionnaires 30
QLQ-OES18	Quality of Life - Supplementary Scale for Esophageal cancer 18
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Stable disease
SOP	Standard operating procedure
SS	Safety set
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TKI	Tyrosine-kinase inhibitor
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
T3	Total triiodothyronine
TTR	Time to response
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
NMPA	National Medical Products Administration

1 Background

1.1 Relevant Background for Esophageal Cancer

Esophageal cancer is the 8th most prevalent cancer in the world. The high incidence regions include Asia, Southern Africa, and Northern France[1]. China is a high incidence region of esophageal cancer. According to the data in the Chinese Cancer Registry Annual Report 2015, among the top 10 most common malignant tumors, esophageal cancer ranked 3rd in males and 5th in females in incidence and ranked 4th in death rate[2]. Esophageal squamous cell carcinoma (ESCC) and adenocarcinoma are the 2 main histological subtypes of esophageal cancer and are the main subtypes in Chinese ESCC, accounting for 90% of the incidence of esophageal cancer[3]. Clinical pathological and epidemiological studies have showed that the main risk factors of ESCC are smoking and alcoholism, and the 2 main risk factors for adenocarcinoma are gastroesophageal reflux disease and Barrett's esophagus[4].

Occurrence of esophageal cancer is a multi-factor, multi-stage complex process, commonly associated with multiple genetic defects. Several studies have demonstrated that the occurrence and evolution of esophageal cancer are related to abnormality of multiple chromosomes. Some studies have found that chromosome 11q13 amplification is the most frequent genetic abnormality in esophageal cancer[41]. Cyclin Dl (CCNDl) is possibly the target gene for 11q13 amplification, suggesting that the gene may possibly play a critical role in the process of esophageal cancer development[41]. The genome characteristics of 11q13 region amplification have been reported in many tumor types including breast adenocarcinoma (15% to 20%), ovarian cancer (16%), bladder cancer (11%), lung cancer (9%), pancreatic adenocarcinoma (14% to 25%), melanoma (9% to 44%), ESCC (33%), and head and neck cancer squamous cell cancer (HNSCC) (30% to 62%)[42]. For the population in Northeastern China, the cancer genetics study for ESCC found that 7 out of 10 tested patients have CCNDl gene overexpression resulting from chromosome 11q13amplication[43]. Another study in 134 Chinese patients with ESCC found that 11q13 amplification is associated with lymphatic metastasis and advanced disease[44]. The study of genetic mutations in esophageal cancer will provide useful information for screening its susceptible genes and may also help with early diagnosis and assessment of prognosis.

For esophageal cancer, the multimodality treatment which may include surgery, radiotherapy, and chemotherapy is generally adopted. The selection of treatment depends on disease stage, tumor site, and patient's medical condition. For early esophageal cancer, surgical treatment

followed by adjuvant chemotherapy has a high response rate; for advanced esophageal cancer, chemotherapy-centered multimodality treatment is the standard care. Commonly used systemic anti-cancer treatment includes 5-Fluorouracil, platinum-based chemotherapy, and taxanes; however, the clinical benefit of such therapy is limited[5].

1.1.1 Targeted Therapy Against Esophageal Cancer

With progress in molecular biological research in cancer, targeted therapy for the treatment of cancer by acting on specific molecules on cancer cells has become an area of great interest in current studies due to high specificity and low toxicity of the targeted therapy.

Presently, some new targeted drugs for treatment esophageal cancer have been clinically explored and applied, including epidermal growth factor receptor (EGFR) inhibitors (e.g., cetuximab and tyrosine-kinase inhibitor [TKI]), human epidermal growth factor receptor-2 (HER-2) inhibitors (e.g., trastuzumab), vascular endothelial growth factor (VEGF) inhibitors (e.g., bevacizumab and certain TKIs), and programmed death receptor-1 (PD-1) inhibitors (e.g., pembrolizumab or nivolumab).[6]

Although targeted drugs, including those directed against EGFR, HER, or VEGF have achieved good clinical efficacy in other solid tumors, the currently available data from the clinical trials in esophageal cancer have showed that the efficacy is not substantial.

1.1.2 Relevant Studies of Programmed Death -1 in Esophageal Squamous Cell Cancer

PD-1 is an immunosuppressive receptor mainly expressed in the surface of T cells, B cells, monocytes, and NK cells, and its relevant ligands are programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2). Here, PD-L1 is extensively expressed in various tumor cells and immune cells, and its expression level may be up-regulated by multiple cytokines (e.g., interferon [IFN]-γ), in tumor microenvironment[7]. The persistent activation of PD-1 pathway following the binding of PD-L1 with PD-1 on the surface of tumor cells and antigen presenting cells may inhibit tumor antigen-specific T cell activation and impair antitumor activities of T cells. PD-1/PD-L1 antibodies may interfere with the binding of PD-L1 and PD-1 and eliminate the immunosuppression of the pathway, thus restoring antitumor immunity of T cells[8].

Pembrolizumab, developed by Merck Sharp & Dohme, was the first PD-1 inhibitor and was approved by the United States Food and Drug Administration (FDA) in 2014 for the

treatment of advanced or unresectable melanoma. The relevant data in the esophageal cancer cohort in KEYNOTE-028 was recently published[9]. The results showed that 90 patients with PD-L1-positive advanced esophageal cancer were enrolled, of whom 23 patients with PD-L1-positive cancer were treated, including 17 patients (74%) with squamous cell cancer, 5 patients with adenocarcinoma, and 1 patient with mucinous adenocarcinoma, whose median follow-up was 7.1 months and response rate was 30.4%, which were all partial response (PR), including adenocarcinoma 40.4% and squamous cell cancer 29.4%; 52.2% of the patients showed evidence of tumor reduction; the median duration of response was 40 weeks; in 6 out of 7 patients, tumor response persisted after discontinuation of the treatment. Common treatment-related adverse events (AEs) included decreased appetite, decreased lymphocyte count, and rashes. There were no treatment-related deaths or AEs requiring discontinuation of treatment. Recently, Phase 2 and Phase 3 studies of Pembrolizumab in patients with esophageal cancer are ongoing in Japan[10].

Nivolumab, developed by Bristol Myers Squibb, was the second PD-1 inhibitor approved by the FDA in 2015 for treatment of metastatic melanoma, and recently has also been approved for treatment of non-small cell lung cancer (NSCLC). The most recent published results from the Study CheckMate-032 of nivolumab showed that the overall response rate of nivolumab monotherapy was 14% in patients with local advanced/metastatic gastric cancer, esophageal cancer, and esophageal junction cancer. The objective response rates in patients with PD-L1 expression >1% and >5% were 27% and 33%, respectively, including 1 patient achieving complete response (CR). The median survival was 5 months, and the 1-year survival rate was 36%[11]. An ongoing Phase 2 study in Japan evaluated safety and efficacy of nivolumab in patients with advanced esophageal cancer. The recently published results showed 17.2% ORR, including 1 patient achieving CR. Twenty-five percent of the patients achieved stable disease (SD). The median overall survival (OS) was 12.1 months. The serious adverse events (SAEs) observed in this study included pulmonary infection, dehydration, and interstitial lung disease[12].

1.2 Background of Toripalimab

The active ingredient of toripalimab, developed independently by Shanghai Junshi Biosciences Co., Ltd. (hereafter referred to as the Sponsor), is a novel recombinant humanized (97% homogeneity) anti-PD-1 monoclonal antibody (China Patent Authorization Code CN104250302B, PCT Patent Publication No. WO2014/206107A1), which is a human

immunoglobin G4/Kappa (IgG4/Kappa) subtype with a point mutation of proline introduced at the No. 228 amino acid site (serine to proline, S228P) in the hinge of IgG4 heavy chain to increase stability of the antibody and reduce possible IgG4 Fab chain replacement. Compared to nivolumab and pembrolizumab which are also anti-PD-1 monoclonal antibodies, Toripalimab differs in the complementarity-determining regions (CDR) and has a unique binding site to PD-1. Toripalimab binds to PD-1 with high affinity and specificity and can effectively block -interaction between PD1 and its ligands, PD-L1 (i.e., B7-H1) and PD-L2 (i.e., B7-DC), thus activating cytotoxic T lymphocytes (CTLs) and inhibiting tumor growth (see the toripalimab Investigator's Brochure for details on the relevant data from the preclinical and clinical studies).[13]

1.2.1 Pharmacodynamics

Toripalimab binds to human PD-1 with high affinity and does not induce complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), or cytokine storm. The in vitro pharmacodynamic study showed that in an antigen memory response experiment, toripalimab could significantly stimulate the proliferation of antigen-specific T cells and enhance the release of IFN-γ. The in vivo pharmacodynamic study showed that toripalimab could effectively increase the proliferation of human cluster of differentiation 4 (CD4+) and CD8+ T cells in the adoptive transfer of human peripheral blood mononuclear cells (PBMC) in an NSG mouse model, while enhancing the activation of human effector/memory T cells, with its stimulation effect obviously more potent than the approved same-target drug nivolumab. Toripalimab can eliminate the immunosuppression of tumor microenvironment on T cells and enhance the killing effect of CTL on tumor cells. In PD-1 humanized mice, toripalimab significantly inhibits the growth of MC38 colon cancer implants.

The PD-1 receptor occupancy test in cynomolgus monkeys showed a dose-effect relationship between toripalimab and PD-1 binding on cell surface, the effective dose started from serum antibody concentration 0.3 μg/mL and became saturated at 3 μg/mL, when the optimal biological effect was exerted. These preclinical data provide justification for dose inference for further conduction of toripalimab clinical studies.

1.2.2 Pharmacokinetics/Pharmacodynamics and Immunogenicity in Animals

Following a single intravenous (iv) infusion of toripalimab at different doses (1, 10, and 75 mg/kg) in cynomolgus monkeys, the serum exposure level increased in a dose-dependent manner within the dose range of 1 to 10 mg/kg. The maximum plasma concentrations (C_{max}) were 27.70±12.29 μg/mL, 216.11±34.52 μg/mL, and 1891.72 ± 270.16 μg/mL in 1, 10 and 75 mg/kg group, respectively. The in vivo half-lives ($t_{1/2}$; 134 to 194 hours) were similar to the reported pharmacokinetic (PK) data of nivolumab and pembrolizumab, and the toripalimab showed low immunogenicity.

1.2.3 Pre-clinical Toxicology Studies

As toripalimab does not bind to murine PD-1, the cynomolgus monkey was selected as the main animal tested for toxicology studies in accordance with the *Guideline on Non-Clinical Safety Evaluation for Therapeutic Biologics*. National Shanghai Center for New Drug Safety Evaluation and Research in China was selected to conduct the preclinical safety toxicology strictly in accordance with Good Laboratory Practice (GLP) requirement. General pharmacology, acute toxicity, chronic toxicity, hemolysis, histological examination, and local irritation studies as well as other nonclinical toxicology studies have been conducted.

General pharmacology: The study evaluating the safety pharmacology of toripalimab found that 10, 30, and 100 mg/kg toripalimab have no obvious effects on cardiovascular system and respiratory frequency in cynomolgus monkeys after iv administration. At the same time, toripalimab has no effect on the motor coordination and behavioral activity in Sprague-Dawley rats.

Acute toxicity: No obvious acute toxicity was observed after a single iv dose of toripalimab to cynomolgus monkeys, and the no observed adverse effect level (NOAEL) was 406 mg/kg, which was approximately 1350 times of the proposed clinical start dose (0.3 mg/kg).

Chronic toxicity: Toripalimab showed no obvious toxicity and side effects in the chronic toxicity experiment of toripalimab in which cynomolgus monkeys were administered iv at the doses of 10, 30, and 100 mg/kg for 4 consecutive weeks. No drug-related abnormal reactions were reported in all the animals. No abnormal changes related to toripalimab were reported in the animals' body weight, food consumption, clinical observations, body temperature, electrocardiogram (ECG), ophthalmologic examinations, clinical pathology (hematology, coagulation function, serum biochemistry, immune function, and urinary and fecal analysis), macroscopic pathology, organ weights, or histopathology. No obvious manifestations of local

stimulation were reported in muscles and blood vessels at the administration site. The in vivo systemic exposure of toripalimab in cynomolgus monkeys was positively correlated to the dose and toripalimab exhibited linear pharmacokinetics after administration of the first dose and non-linear pharmacokinetics after administration of multiple doses.

In the chronic toxicity experiment in cynomolgus monkeys after iv injection of 10, 30, and 100 mg/kg toripalimab for 26 consecutive weeks, no abnormal changes related to toripalimab were observed in body weight, food consumption, clinical observations, body temperature, ECG, ophthalmologic examinations, clinical pathology (hematology, coagulation function, serum biochemistry, immune function, and urinary and fecal analysis), hormone levels (testosterone or free testosterone), macroscopic pathology, organ weight or histopathology, or immunohistopathology. The NOAEL was 100 mg/kg. The systemic exposure of toripalimab was positively correlated with the dose and has a linear kinetic property. After administration of toripalimab for 26 consecutive weeks, obvious accumulation was observed at the moderate and high doses and not at the low dose.

Hemolysis: After addition of different doses of toripalimab (the proposed C_{max} was ≤3 mg/mL) to rabbits' red blood cells, toripalimab, at the dose of 10 mg/mL, did not result in hemolysis and condensation of rabbits' red blood cells.

Local stimulation: The experiment in cynomolgus monkeys was a concurrent experiment consisting of a 4-week iv administration and a 4-week recovery period. The experimental results showed that during and after toripalimab administration（2, 6, and 20 mg/mL), no swelling, hemorrhage, infection, induration, or necrosis occurred at the injection sites across the animal groups. Histopathology examinations showed no obvious pathological changes in blood vessels and muscle tissues at the administration sites.

Genotoxicity: In accordance with the "General Principles for Technical Evaluation of Nonclinical Safety of Therapeutic Biological Products" and the Nonclinical Safety Evaluation of Drugs for Biotechnology Application (Mar 23, 2012), toripalimab is a macromolecular drug and would not interact directly with deoxyribonucleic acid (DNA) or other chromosome substances; thus, no genetic toxicity studies were conducted.

Carcinogenicity: In accordance with the General Principles for Technical Evaluation of Nonclinical Safety of Therapeutic biological Products and the Guideline for Nonclinical Evaluation of Antineoplastic Drugs (Mar 4, 2010), toripalimab is a drug developed

specifically for patients with advanced cancer; thus, no carcinogenicity studies were conducted.

Reproductive and developmental toxicity: In accordance with the General Principles for Technical Evaluation of Nonclinical Safety of Therapeutic biological Products, and the Nonclinical Safety Evaluation of the Drugs for Biotechnology Application (Mar 23, 2012), toripalimab is used in clinical studies for treatment of tumor; thus, no reproductive and developmental toxicity study was conducted. According to literature reports, it is known that PD-1/PD-L1 signal pathway is critical for maintenance of pregnancy and for fetal tissue resistance and embryo-fetal survival via maternal immunity (Guleria et al. 2005; Habicht et al. 2007; D'Addio et al. 2011). It is expected that toripalimab has an adverse effect on pregnancy and has a risk to human fetuses, including embryonic death. In principle, toripalimab is not applicable for pregnant women or women who plan to be pregnant.

1.3 Toripalimab-related Clinical Experience

1.3.1 Ongoing Clinical Studies

Currently, there are several ongoing and planned studies of toripalimab to evaluate efficacy and safety of the monotherapy or in combination with other drugs. By August 31, 2018, nearly 900 patients had been enrolled across 18 Phase 1 to 3 clinical studies. The complete list of ongoing studies is provided in Table 1.

Table 1 List of Ongoing Clinical Studies of Toripalimab

No.	Study code	Trial name	Progress
CT1	HMO-JS001-I-CRP-01	A phase 1, open, single-center, dose-escalation study to investigate the tolerability and pharmacokinetics of single dose and multiple doses of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in patients with advanced tumors	Enrollment closed
CT2	JS001-I-CRP-1.4	Phase 1a clinical study on the safety, tolerability, pharmacokinetics, and pharmacodynamics of single dose combined with multiple doses of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in patients with advanced solid tumors	Enrollment closed
CT3	JS001-I-CRP-1.3	A phase 1 clinical study on the safety, tolerability, pharmacokinetics, and pharmacodynamics of single dose and multiple doses of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in patients with advanced malignant tumors	Enrollment closed
CT4	HMO-JS001-II-CRP-01	An open-label, multi-center, single-arm, phase 2 clinical study to investigate the efficacy and safety of	Enrollment closed

No.	Study code	Trial name	Progress
		Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in patients with locally advanced or metastatic melanoma after failure of standard of care	
CT5	JS001-Ib-CRP-1.0	A Phase 1b/2, multi-center, open-label clinical study to evaluate JS001 in treatment of advanced gastric adenocarcinoma, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, and head and neck squamous cell carcinoma	Enrollment ongoing
CT6	JS001-I	A phase 1 clinical study on the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in patients with recurrent refractory malignant lymphoma	Enrollment closed
CT7-1	HMO-JS001-I-PK-01	A phase 1 study to investigate the similarity in pharmacokinetics and safety of single-dose and parallel comparison of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection Before and After the Process Change in patients with advanced NSCLC before and after process change	Enrollment closed
CT 7-2	HMO-JS001-I-PK-02	A phase 1 study to investigate the similarity in pharmacokinetics and safety of single-dose and parallel comparison of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection Before and After the Process Change in patients with advanced melanoma before and after process change	Enrollment closed
CT8	HMO-JS001-II-MM-02	A randomized, controlled, multi-center, phase 2 clinical study to investigate Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection vs high-dose interferon in adjuvant therapy of completely resected mucosal melanoma	Enrollment ongoing
CT9	HMO-JS001-I-CRP-03	An open-label, single-center, dose-escalation, phase 1 clinical study to investigate the tolerability and pharmacokinetics of single and multiple doses of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in patients with triple negative breast cancer	Enrollment closed
CT10	HMO-JS001-I-CRP-1.4	A prospective phase 1 clinical study on radiotherapy combined with Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection (JS001) in treatment of advanced triple negative breast cancer	Enrollment ongoing
CT11	HMO-JS001-I-CRP-1.5	A phase 1 clinical trial on Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection (JS001) in combination with Gemcitabine plus Cisplatin (GP) as the first-line therapy for advanced triple negative breast cancer	Not initiated but closed
CT12	HMO-JS001-II-CRP-02	An open-label, multi-center, single-arm, phase 2 clinical study to investigate the efficacy and safety of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in patients with locally advanced or	Enrollment ongoing

No.	Study code	Trial name	Progress
		metastatic bladder urothelial carcinoma after failure of standard of care	
CT13	HMO-JS001-Ib-CRP-01	An open, single-center, dose-escalation, phase 1b clinical study to investigate the tolerability and pharmacokinetics of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection combined with Axitinib in patients with advanced renal carcinoma and melanoma after failure of standard of care	Enrollment ongoing
CT14	HMO-JS001-Ib-NEC-02	A phase 1b clinical study to investigate the safety and efficacy of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in patients with advanced neuroendocrine tumor after failure of standard of care	Enrollment ongoing
CT15	JS001-NPC-III	A randomized, double-blind, international, multi-center, phase 3 study to evaluate the efficacy and safety of JS001/placebo combined with GP regimen (Gemcitabine and Cisplatin) in treatment of advanced nasopharyngeal carcinoma	Initiating
CT16	JS001-016-II-HCC	A randomized, double-blind, multi-center, phase 2 study to evaluate the efficacy and safety of recombinant humanized anti-PD-1 monoclonal antibody (JS001) as the postoperative adjuvant therapy for patients receiving radical resection of high-risk recurrent liver cancer	Initiating
CT17	JS001-017-III-MM	A randomized, controlled, multi-center, phase 3 clinical study to investigate Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection (JS001) vs Dacarbazine as the 1st-line therapy for unresectable or metastatic melanoma	Enrollment ongoing
CT18	JS001-018-II-LC	A multi-center, single-arm phase 2 clinical study to evaluate JS001 combined with Pemetrexed and carboplatin in treatment of advanced or recurrent non-small cell lung cancer with EGFR sensitive mutation and negative T790M after failure of EGFR-TKI therapy	Enrollment ongoing

1.3.2 Clinical Safety

According to the Investigator's Brochure (IB), the safety profile of toripalimab is summarized for 598 patients with different types of tumors (including melanoma, nasopharyngeal carcinoma, ESCC, gastric adenocarcinoma, head and neck squamous cell carcinoma, NSCLC, triple negative breast cancer, malignant lymphoma, and soft tissue sarcoma, etc.) by August 2018.

A total of 576 of 598 (96.3%) patients had at least 1 AE, and 556 (93.0%) patients had an AE related to toripalimab. The most commonly reported (≥10%) treatment-emergent adverse events were anemia, elevated alanine aminotransferase (ALT), elevated aspartate

aminotransferase (AST), fever, cough, decreased white blood cell count, rash, decreased appetite, weakness, and hypothyroidism. Eighty-eight (14.7%) patients had an SAE related to toripalimab that occurred in ≥4 (0.7%) patients, including pulmonary infection in 10 (1.7%) patients, death in 8 (1.3%) patients, pneumonia in 6 (1.0%) patients, and decreased platelet count in 5 (0.8%) patients. Seventy-eight (13.0%) patients had AEs related to toripalimab that led to termination of the drug. Fifty-two (8.7%) patients had AEs related to toripalimab that led to interruption of the drug. One hundred forty-two (23.7%) patients had grade 3 and above AEs related to toripalimab and those occurred in ≥4 (0.7%) patients included anemia and hyponatremia each in 16 (2.7%) patients; elevated lipase in 9 (1.5%) patients; death in 8 (1.3%) patients; pulmonary infection in 7 (1.2%) patients; elevated amylase and elevated AST each in 6 (1.0%) patients; elevated ALT in 5 (0.8%) patients; and decreased platelet count, elevated serum triglyceride, elevated γ-glutamyl transferase, hypokalemia, hyperuricemia, fatigue, hypertension, and pneumonia each in 4 (0.7%) patients.

Immune-related adverse reaction was observed in 155 (25.9%) patients and included immune-related interstitial lung disease, immune-related hypothyroidism and hyperthyroidism, immune-related pancreatitis, immune-related hyperglycemia or diabetes, immune-related abnormal hepatic function, and immune-related adrenal cortical insufficiency, which were mostly grades 1 to2 and did not lead to termination or interruption of toripalimab and were completely relieved for most of them. These adverse reactions were consistent with those observed for other similar products and no new immune-related adverse reaction was found.

Overall, the AEs observed in the pooled safety data are mainly abnormalities in various examinations, mostly grades 1 to2 in severity or consistent with the characteristics of underlying disease. The immune-related adverse reactions are consistent with that reported for products in the same class and showed a good tolerability. No new safety signal is seen. The AEs are overall controllable.

Please see the Investigator’s Brochure for the details.

1.3.3 Clinical Efficacy

Study HMO-JS001-II-CRP-01 (CT4) was a Phase 2, open-label, multi-center, single-arm clinical study to investigate the efficacy and safety of toripalimab 3 mg/kg every 2 weeks (Q2W) in the treatment of patients with locally advanced or metastatic melanoma after failure

of standard of care. The primary endpoint was the objective response rate evaluated by independent radiological data review committee in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. By the data cutoff date of March 15, 2018, a total of 128 patients with locally progressed or metastatic melanoma after failure of previous treatment had been enrolled. As per RECIST 1.1, the evaluation by the independent third-party review committee showed that in the efficacy evaluable population, 1 (0.83%) patient had CR, 21 (16.54%) patients had PR, 51 (40.16%) patients had SD, and 48 (37.80%) patients had progression of disease (PD); the ORR was 17.32% (95% confidence interval [CI]: 11.19, 25.04%) and the disease control rate (DCR) was 57.48% (95% CI: 48.40, 66.20%). An analysis of duration of response (DOR) showed that by the data cutoff date, 21 out of 22 patients with CR or PR had ongoing responses and the median DOR was not reached. The DOR ranged from 1.87+ to 10+ months and all patients were censored for DOR. The analysis of time to response (TTR) showed that among the 22 out of 127 patients who had CR or PR, the median TTR was 3.45 months (95% CI: 1.74, 3.57) and the TTR ranged from 1.61 to 7.34 months. The median progression-free survival (PFS) was 3.61 months (95% CI: 2.72, 5.48 months). The longest PFS was 13.61 months, and the 6-month PFS rate was 34.89%. The OS data were immature (107 out of 127 patients were censored) and had not yet reached the median OS, with the longest survival of 14.52 months, a 6-month survival rate of 88.87%, and a 12-month survival rate of 78.97%.

Study JS001-Ib-CRP-1.0 (CT5) was a multi-center Phase 1b/2 clinical study (basket trial) intended to preliminarily evaluate the antitumor activity and tolerability of toripalimab in the treatment of advanced gastric adenocarcinoma, ESCC, nasopharyngeal carcinoma, and head and neck squamous cell carcinoma and provide a basis for the subsequent Phase 3 clinical study. The primary endpoint was the ORR evaluated by the investigator in accordance with RECIST 1.1. As of November 30, 2017, the results evaluated by the investigator according to the RECIST 1.1 in the interim analysis showed CR in 1 patient (esophageal cancer), PR in 35 patients, and ORR of 22.4%, based on the evaluable-evaluable population across all cohorts. A total of 44 (27.3%) patients had SD and the DCR was 49.7% in the overall efficacy-evaluable population. There were 8 patients with PR in the patients with gastric adenocarcinoma, and the ORR was 20.0%; there was 1 patient with CR and 9 patients with PR among the patients with ESCC, and the ORR was 20.8%; there were 14 patients with PR among the patients with nasopharyngeal carcinoma, and the ORR was 28.0%; there were 4

patients with PR among the patients with head and neck squamous cell carcinoma, and the ORR was 17.4%.

Please see the Investigator's Brochure for the details.

1.3.4 Clinical Pharmacokinetics, Dose Selection, and Immunogenicity

The preliminary PK data show a linear PK profile of toripalimab within the range of 0.3 to 10 mg/kg; when the dose is 10 mg/kg, toripalimab shows a non-linear PK profile in some but not all clinical studies. The plasma drug concentration basically reached steady state in patients after toripalimab iv infusion for 3 to 4 consecutive doses; in vitro experiments showed when the concentration of toripalimab was >20 nM or 3 μg/mL, it saturates PD-1 receptors on the T cell surface. Peripheral blood concentrations of toripalimab are at 25 μg/mL may ensure entry of antibody macromolecules into the tumor microenvironment. At the dose of 3 mg/kg Q2W, the minimum plasma drug concentration at steady state ranges from 20 to 40 μg/mL. In addition, all Phase 1 studies showed complete occupancy of PD-1 receptors at all dose groups (0.3, 1, 3, and 10 mg/kg, once Q2W). The above-stated PK results and data on receptor occupancy support the selection of dose regimen of 3 mg/kg once Q2W as the dose for the CT4 Phase 2 pivotal study.

A fixed dose of 360 mg, Q3W, was explored in 2 early studies (CT5 and CT7). The preliminary PK results from 9 patients in these 2 studies showed that, compared to 3 mg/kg Q2W (from the 11 patients in CT1), the steady-state peak concentration increased by 153% (166.53 ug/mL: 95% CI: 121.0, 212.0 vs 108.83 ug/mL: 95% CI: 87.5, 130.0); the steady-state peak concentration increased by 133% (47.92 ug/mL: 95% CI: 31.8, 64.0 vs 36.09 ug/mL: 95% CI: 27.7, 44.5), and $AUC_{0\text{-}Day85}$ increased by 138% (164993 ug/mL×h vs 119814 ug/mL×h). The PK model predicted a similar trough concentration (~32 ug/mL) and exposure level for 240 mg Q3W and 3 mg/kg Q2W. Based on a comprehensive consideration of the above - results of toripalimab PK, receptor occupancy data and the results from the CT 4, a phase 2 study in patients with previously treated melanoma, toripalimab 240 mg Q3W was recommended as the dose for Phase 3 clinical studies.

Additionally, the PK data in the single dose and multiple dose periods of CT1 showed that, after administration of multiple doses, toripalimab has accumulation in human body, while in the previous dose-escalation study, 0.3 to 10 mg/kg showed no dose-limiting toxicity (DLT)

and exhibited a good tolerance. These results further supported the recommended dose for clinical Phase 3 studies, i.e., toripalimab 240 mg fixed dose, Q3W.

The use of any recombinant protein has the potential to induce local and systemic immune responses. Additional tests, such as autoimmune serology or biopsy, should be used to carefully monitor the patient for development of anti-drug antibodies (ADAs) to determine the probability of possible immunogenicity and the impact on the patient.

The results of a pooled analysis from 518 patients showed that ADA development was observed in all patients receiving toripalimab at doses ranging from 0.3 to 10 mg/kg and the ADA-positive rate of individual patients was 17.2%. The ADA-positive rate of individual patients was 18% among 128 melanoma patients who received toripalimab 3 mg/kg. Based on PK and exposure-efficacy analyses, no loss of efficacy, change in toxicity profile, or change in PK profile were observed in the presence of ADAs, and no difference in efficacy and safety was observed between ADA-positive and -negative patients.

The incidence of ADA is highly dependent on the sensitivity and specificity of the assay. In addition, the positive rate of antibodies (including neutralizing antibodies) detected in the trial will also be affected by other factors, including analysis methods, sample processing, sample collection time, concomitant drug therapy, and other concomitant diseases. For these reasons, comparison of ADA rates between different products may be misleading. The current amount of data is insufficient to conclude the correlation between ADA and drug exposure, safety, and efficacy. In the future, collection and analysis of plasma concentration and ADAs should be continued in clinical trials, and subsequent analysis of ADA and its correlation with drug exposure, efficacy, and safety should be carried out.

Please see the IB for details.

1.4 Rationale for Study Design

Rationale for evaluation of toripalimab in combination with the TP regimen in patients with esophageal cancer:

Cisplatin is a first-generation platinum-based antitumor drug. A cisplatin-based regimen is generally used for treatment of patients with advanced or metastatic esophageal cancer. Cisplatin-based combination regimens generally include combinations with taxanes, vinorelbine, and gemcitabine and show good efficacy in the treatment of advanced, relapsed, and metastatic esophageal cancer.

Paclitaxel is an anti-microtubular drug. It arrests cells at G2 phase and mitotic phase and has significant efficacy against multiple cancer cells. The overall response rate of paclitaxel monotherapy in treatment of patients with esophageal cancer may be 17% to 31% and paclitaxel has no cross resistance with cisplatin.

In a Phase 2 clinical study, paclitaxel plus cisplatin were used in the treatment of 35 patients with advanced esophageal cancer. The results of this study showed that the overall response rate was 48.6%, including 45.7% achieving PR, the median PFS was 7 months, the median survival was 13 months, and the 1-year survival rate was 39%; no SAEs were reported[18]. In another paclitaxel plus cisplatin study to treat patients with advanced esophageal cancer, the overall response rate was 37.3%. The response rates in the initial treatment group and the retreatment group were 40.5% and 28.6%, and CR rates were 5.4 and 7.1%, respectively. In the study, the major toxicity was grades 3 to 4 bone marrow suppression, which resolved in all patients [19]. In a study that compared the efficacy and safety of paclitaxel to 5-fluorouracil plus cisplatin therapy as first-line therapy in treatment of the patients with advanced ESCC[20], the ORR of paclitaxel plus cisplatin and of 5-fluorouracil plus cisplatin were 42.5% and 38.4%, median PFS times were 7.85 and 6.53 months that showed statistically significant difference, and the median OS times were 13.46 and 12.67 months, respectively.

Based on the above 2 clinical studies, the combination regimen of paclitaxel plus cisplatin for treatment of patients with advanced esophageal cancer has confirmed efficacy and is tolerable. It is expected that toripalimab plus paclitaxel and cisplatin in treatment of advanced or metastatic ESCC may further increase efficacy and benefit patients.

Rationale for biomarker assessment:

In CT5, a Phase 1b/2, open-label, multi-center, clinical study evaluating toripalimab in treatment of advanced gastric adenocarcinoma, ESCC, nasopharyngeal cancer, and head and neck squamous cell cancer, the whole-exome sequencing found that 24 out of 51 (47.1%) patients with ESCC in the toripalimab monotherapy group carried 11q13 segment amplification; patients without 11q13 segment amplification achieved better results in terms of objective response rate, median PFS, and median OS than the patients with 11q13 segment amplification.

1.5 Benefit-Risk Assessment

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that a focus on the treatment of improving T cell response to cancer may lead to significant survival benefit for patients with advanced malignancies. Therefore, immunomodulation is a new and promising cancer therapeutic strategy and may improve anticancer activity. When chemotherapeutic drugs are used alone, they may kill tumor cells by cytotoxicity, but can also result in exposure of the immune system to high-level tumor antigens. When chemotherapeutic drugs and PD-1/PD-L1 inhibitors are used concurrently, they may increase immune activities of tumor-specific T cells by inhibiting PD-L1/PD-1 signal pathway to produce deeper and longer response effects[16],[17].

The results of the preclinical pharmacodynamic study showed that toripalimab can activate T lymphocytes and has significant inhibition of tumor growth in NSG mice when combined with CTL. In the head-to-head in vitro and in vivo pharmacodynamic studies with nivolumab, toripalimab showed favorable pharmacodynamic characteristics (better PD-1 binding) and displayed an excellent safety profile in the long-term toxicity trial in primates. No DLT is observed from the present toripalimab human study data, and its safety is in the acceptable range. With reference to the research results of the same type of drugs, nivolumab and pembrolizumab, it is expected that toripalimab has similar risk and benefits.

Esophageal cancer is a highly prevalent malignancy in China; the risk factors for development of esophageal cancer may be different from those in other regions of the world. In China, patients with esophageal cancer are generally mostly at advanced stage when diagnosed, and the tumor burden are heavier than those in developed countries. Thus, there is an urgent clinical need in China. The ongoing Phase 1 to Phase 2 clinical studies in ESCC in Chinese patients evaluate safety of toripalimab at different doses. Although toripalimab is generally well tolerated (see Section 1.3.2), immune-related adverse events (irAEs) are still observed in Study JS001-Ib-CRP-1.0, including hypothyroidism, fever, decreased triiodothyronine (T3), and increased thyroid stimulating hormone (TSH), etc. However so far, those events may be managed through treatment. The early clinical study of toripalimab provides adequate evidence for the further conduction of Phase 3 clinical study of toripalimab in patients with esophageal cancer to explore the efficacy of toripalimab in Chinese patients with esophageal cancer.

Through the study design and the toxicity management guideline for chemotherapeutic drugs and immune/infusion-related AEs, toxicities of toripalimab, as monotherapy or in

combination with other cancer therapy, are usually manageable. Toripalimab maintains good benefit-risk characteristics, which supports clinical development for this indication.

2 Study Objectives

This study is intended to evaluate efficacy and safety of toripalimab in combination with paclitaxel and cisplatin (hereafter referred to as TP regimen) vs placebo in combination with the TP regimen in patients with advanced or metastatic ESCC who have not received systemic chemotherapy previously.

2.1 Efficacy Objectives

2.1.1 Primary Efficacy Objective

The primary objective of this study is:

1) To evaluate and compare differences in PFS (as assessed by the blinded independent central review [BICR] per RECIST 1.1) and OS following toripalimab in combination with the TP regimen vs placebo in combination with the TP regimen in all randomized patient population with advanced or metastatic ESCC who have not received systemic chemotherapy previously.

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives of the study are:

2) To evaluate differences in efficacy of toripalimab in combination with the TP regimen vs placebo in combination with the TP regimen in terms of measuring indicators ORR, DCR, DOR, and TTR as evaluated by the investigator and by the BICR in accordance with RECIST 1.1

3) To evaluate differences in efficacy of toripalimab in combination with the TP regimen vs placebo in combination with the TP regimen in terms of measuring indicator PFS as evaluated by the investigator in accordance with RECIST 1.1

4) To evaluate differences in efficacy of toripalimab in combination with the TP regimen vs placebo in combination with the TP regimen in terms of measuring indicators ORR, DCR, DOR, and TTR as evaluated in accordance with Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

5) To evaluate 1- and 2-year PFS rates of the treatment groups

6) To evaluate 1- and 2-year OS rates of the treatment groups

7) To evaluate disease-related symptoms and Health-Related Quality of Life in patients receiving toripalimab in combination with the TP regimen vs placebo in combination with the TP regimen by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life - Core Questionnaires 30 (QLQ-C30) and Quality of Life - Supplementary Scale for Esophageal cancer 18 (QLQ-OES18) questionnaires.

2.2 Safety Objective

To evaluate safety and tolerance in all randomized patients receiving toripalimab in combination with the TP regimen vs placebo in combination with the TP regimen.

2.3 Exploratory Objectives

1) To explore the correlation between the biomarkers in archived or fresh tissue specimen and blood (including but not limited to PBMC, PD-L1, Epstein-Barr virus (EBV), microsatellite instability (MSI), 11q13, tumor mutation burden, and other) and disease status, mechanism of drug resistance, and/or response to toripalimab.

2) To evaluate the incidence and titer of ADA against toripalimab and to explore the potential correlations between the immunogenicity response and PK, safety, and efficacy

3) To evaluate the feasibility of biopsy in patients with PD to differentiate between an increase of tumor volume due to immunoregulatory activity of toripalimab (i.e., pseudoprogression/tumor immune infiltration) and the true PD.

3 Study Design

3.1 Study Description

This is a randomized, double-blind, multi-center, placebo-controlled, Phase 3 study. The objective of this study is to compare the efficacy and safety of toripalimab combined with a TP regimen with placebo combined with a TP regimen in approximately 500 patients with advanced or metastatic ESCC who have not previously received systemic chemotherapy. The detailed study design is shown in Figure 1. For the assessment schedule, please see the Study Flow Sheet in Appendix 1Schedule of Assessments.

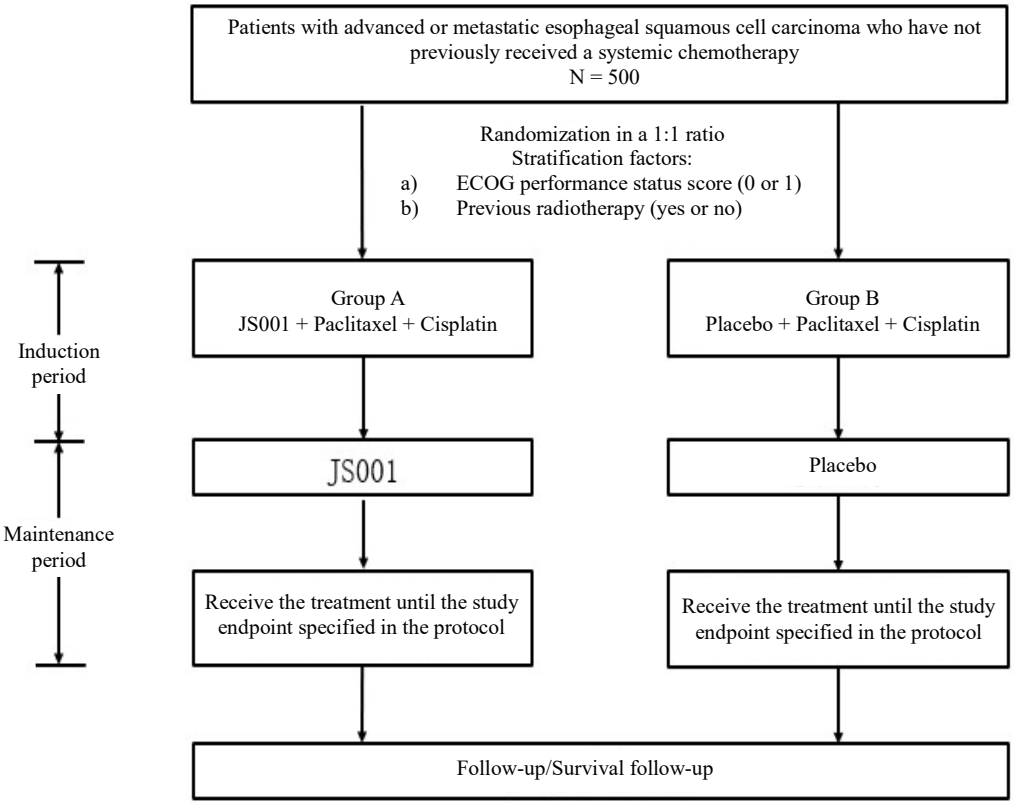


Figure 1 Study Flowchart

Eligible patients will be randomized 1:1 into Group A (toripalimab combined with TP regimen) or Group B (placebo combined with TP regimen). The stratification factors include Eastern Cooperative Oncology Group (ECOG) performance status score (0 or 1) (see Appendix 9) and previous radiotherapy (yes or no). The treatment plan will include an induction period and a maintenance period in this study. Patients will receive toripalimab or placebo combined with a TP regimen in the induction period in 1 treatment cycle of 3 weeks for up to 6 cycles. Dosing will occur on Day 1 of each cycle; Day is defined as the first day the patient will receive the study drug. Thereafter, patients will enter the maintenance period to receive toripalimab or placebo monotherapy on Day 1 of each three--week cycle (Table 2)

Table 2 Treatment Groups

Treatment group	Induction period (3 weeks/cycle for up to 6 cycles, dosing on Day 1 of each cycle)	Maintenance period (3 weeks/cycle, dosing on Day 1 of each cycle)
Group A	Toripalimab (240 mg), paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2)	Toripalimab (240 mg)
Group B	Placebo (240 mg), paclitaxel (175 mg/m^2), and cisplatin (75 mg/m^2)	Placebo

Study drug will continue until intolerable toxicity, PD, patient refusal to continue study drug treatment, judgment by investigator that the patient needs to be withdrawn from the treatment, or up to two years of treatment, whichever occurs first. During the treatment, if one or both of the chemotherapeutic agents is/are discontinued due to toxicity, the study drug treatment will continue. If PD occurs (in accordance with RECIST 1.1) and the patient may still clinically benefit from continuation of the drug administration as judged by investigators, the patient can continue toripalimab (Group A) or placebo (Group B) treatment after discussion between the Investigators and the Sponsor on the comprehensive benefit-risk ratio and the patients' signing of informed consent form. The potential for clinical benefit is based on a comprehensive evaluation of radiological findings and clinical status by the investigator and the absence of intolerable toxicity or worsening of symptoms due to PD. Patients who discontinue study drug administration will be followed for survival (i.e., using the date of the last dose as a starting point). Data on any subsequent antitumor therapy and survival will be collected every 3 months (±7 days) until death, withdrawal of informed consent, loss to follow-up, or termination of the study by the Sponsor, whichever occurs first.

Patients with stable disease or a complete (CR) or partial response (PR) as determined by the investigator will discontinue the study treatment after receiving toripalimab treatment for up to 2 years. If PD occurs in these patients after discontinuation of study drug in these patients, the investigators should discuss with the medical monitor whether the patient can resume the study drug provided that the following criteria are met:

- No other antitumor therapies were administered after the last dose of study drug.
- All general inclusion criteria listed in Section 4.1.1 are met and none of the exclusion criteria in Section 4.1.2 are met.

During the study, investigators will evaluate tumors in accordance with RECIST 1.1 (see Appendix 4 for details) and irRECIST (see Appendix 5 for details).

Regardless of any delay in study treatment dosing, the patient will receive tumor evaluation at baseline (screening period) and once every 6 weeks (±7 days) in the first 12 months of treatment. After 12 months, the tumor will be evaluated once every 9 weeks (±7 days) until intolerable toxicity, PD, patient refusal to continue study drug treatment, judgment by investigator that the patient needs to be withdrawn from the treatment, or up to two years of treatment, whichever occurs first. Management of all patients will be based on investigator assessment.

Tumor evaluation must be conducted once every 6 weeks (±7 days) in the first 12 months after the start of treatment, and thereafter once every 9 weeks (±7 days), for patients who terminate the treatment for any reason other than PD (e.g., toxicity), until PD, death, withdrawal of consent to remain on study, loss to follow-up, termination of the study by the Sponsor, or start of a new antitumor therapy, whichever occurs first.

Patients who are suspected of having PD prior to the next scheduled tumor evaluation should undergo an unscheduled tumor evaluation.

If a patient withdraws consent to continue study drug therapy for any reason, an imaging examination must be during the end-of-treatment visit. If the previous imaging examination was performed within 28 days of the request for discontinuation of study drug treatment, it does not need to be repeated. The mode of imaging scan (CT or MRI) should be the same as that performed at baseline, including scanning layer thickness and contrast media.

At the time of PD, a tumor biopsy will be obtained (after obtaining patient consent via signing of the informed consent form). If a tumor biopsy sample is not collected, the reason why the biopsy was not collected must be recorded in the electronic case report form (eCRF).

Tumor specimens collected at enrollment and disease progression will be tested for expression of PD-L1 and other exploratory biomarker studies in the central laboratory. Tumor biopsy data obtained at the time of PD will be used during the exploratory investigations to ascertain the consistency between radiological findings and evidence of true progression. In addition, the data from tumor biopsy will be analyzed to evaluate the correlation between changes in biomarkers and the clinical outcome and to understand the mechanisms of PD and drug resistance in patients of toripalimab arm by comparing with chemotherapy arm. Evaluation of the exploratory biomarkers will not be used for the development of any treatment-related strategy.

Patients who cannot safely undergo a tumor biopsy nor provide a sample for biopsy but otherwise meet the above criteria can continue study drug treatment. Patients who cannot safely undergo a tumor biopsy nor provide a sample for biopsy but otherwise meet the above criteria can continue study drug treatment.

The Independent Review Committee (IRC), which is composed of independent experts, will conduct a blinded independent review, in accordance with RECIST 1.1 and irRECIST, of all radiological scans and determine the PFS, ORR, DOR, and DCR results. Refer to the corresponding IRC charter for details on this review.

Considering the unique responses observed (such as delayed response after pseudo-progression) with cancer immunotherapy, both RECIST 1.1 and irRECIST will be used to evaluate the tumor response. A treatment duration of 2 years is considered as sufficient to provide the maximum therapeutic effect. Therefore, in the induction period, patients who achieve an objective response (CR or PR) or have stable disease will continue study drug as maintenance therapy for up to 2 years. After 2 years, patients should receive best supportive caret or start a new anti-cancer treatment according at the time of disease progression.

This study will be conducted in accordance with national and international ethical standards and Good Clinical Practice (GCP). This protocol will be approved by the ethics committee (EC) of the participating centers.

3.2 End of study and Duration of the Study

The end of this study is defined as the time needed to observe approximately 366 deaths for the primary analysis of OS in the intent-to-treat (ITT) population. The duration of this study is estimated to be approximately 39 months from the first patient signing the ICF to the end of the study. If there are patients who are still receiving the study drug at the end of study, they will be transferred to an extension study to continue to receive toripalimab.

If there are patients who are still receiving the study drug at the end of the study, they will be transferred to an extension study to continue to receive toripalimab until intolerable toxicity, PD, patient refusal to continue study drug treatment, judgment by investigator that the patient needs to be withdrawn from the treatment, or up to two years of treatment, whichever occurs first. The Sponsor may make the decision to terminate the study at any time.

4 Study Population, Randomization Scheme, Treatment and Monitoring Plan

4.1 Study Population

The study plans to enroll approximately 500 patients with advanced or metastatic ESCC who have not received previously a systemic chemotherapy.

4.1.1 Inclusion Criteria

For inclusion in the study, patients must fulfill all the following criteria:

1. Inclusion criteria for esophageal cancer:

    a) Histologically or cytologically confirmed, locally advanced/relapsed or metastatic ESCC that cannot be eradicated;

    b) No prior systemic antitumor therapy for relapsed or metastatic tumor;

    c) No relapse in an interval of at least 6 months after the end of the last dose in the patients previously receiving adjuvant, neoadjuvant chemotherapy/radiotherapy/ chemoradiotherapy and radical therapy for non-metastatic disease (no relapse at least 12 months after the end of the last dose in patients previously receiving adjuvant chemotherapy/chemoradiotherapy with a TP regimen);

    d) No risk of major hemorrhage or esophageal fistula, for example, a patient with a large ulcer at the lesion would not be suitable to for enrollment, as the lesion is considered a risk for major hemorrhage and esophageal fistula. The enrollment eligibility of those patients who are at risk of hemorrhage or fistula due to direct ESCC invasion of adjacent organs, e.g., aorta or trachea (T4b disease) should be determined in consultation with the Sponsor. The Sponsor will make the final decision on eligibility.

2. General requirements for inclusion:

    a) Signed informed consent;

    b) Male or female aged 18 to 75 years;

    c) ECOG performance status score of 0 or 1;

    d) Expected survival longer than 3 months;

    e) Agreement to provide a previously reserved tumor tissue specimen or biopsied tumor lesion tissue for biomarker analysis;

f) At least 1 measurable lesion in accordance with RECIST 1.1 (only when clear PD occurs after radiotherapy for a previously irradiated lesion can a lesion be used as a measurable lesion);

g) Adequate organ function as defined below:

- Hematology: Neutrophil $\geq 1.5\times10^9$/L, hemoglobin ≥9 g/dL, and platelet $\geq 100\times10^9$/L;
- Hepatic function: bilirubin ≤1.5× upper limit of normal (ULN) (patients who are known to have Gilbert's syndrome and have a serum bilirubin level ≤3× ULN can be enrolled), AST and ALT ≤2.5× ULN (in case of hepatic metastasis, AST /ALT ≤5× ULN), and alkaline phosphatase (ALP) ≤3× ULN (in case of hepatic or bone metastasis, ALP ≤5× ULN); albumin ≥3 g/dL;
- International normalized ratio (INR) or prothrombin time (PT) or activated partial thromboplastin time (aPTT) ≤1.5× ULN;
- Renal function: Serum creatinine ≤1.5× ULN or estimated glomerular filtration rate by Cockcroft-Gault formula: Creatinine clearance (CrCL) ≥60 mL/min

$$\frac{(140 - \text{age}) \times (\text{body weight, kg}) \times (0.85, \text{for females})}{72 \times (\text{serum creatinine, mg/dL})}$$

or:

$$\frac{(140 - \text{age}) \times (\text{body weight, kg}) \times (0.85, \text{for females})}{0.818 \times (\text{serum creatinine, } \mu\text{mol/L})}$$

h) Female patients who meet the following criteria are eligible for inclusion in the study:

Female patients with no childbearing potential (e.g., physiologically infertile), based on any of the following criteria:

- Hysterectomy performed;
- Bilateral oophorectomy (oophorectomy) performed;
- Bilateral tubal ligation performed; or

- Postmenopausal (menopause ≥1 year).

Female patients with childbearing potential who have a negative serum pregnancy test result at screening (within 7 days prior to the first dose of the investigational drug) and use adequate contraceptive measures prior to the study until 60 days after the last dose of the investigational drug.

Adequate contraceptive measures taken continuously, according to the instruction on the contraceptive product and physician's guidance, are defined as follows:

- Any intrauterine device confirmed to have a failure rate for contraception lower than 1% per year;
- Dual-barrier contraception, defined as a condom with spermicidal gel, foam, suppository, or film; a diaphragm with spermicide; or a male condom used in combination with a diaphragm.

4.1.2 Exclusion Criteria

Patients who fulfill any of the following criteria will be excluded from this study:

1. Cancer-specific exclusion criteria:

   a) Active or untreated central nervous system (CNS) metastasis (e.g., brain or leptomeningeal metastasis) confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI) evaluation at screening and previous radiological evaluation. Patients who have previously received treatment of brain or leptomeningeal metastases, have stabilized for ≥2 months, and have discontinued systemic hormone therapy (>10 mg/d of prednisone or equivalent) for >28 days prior to randomization may participate in the study;

   b) Uncontrolled tumor-related pain;

   c) Uncontrolled pleural effusion, pericardial effusion, or ascites requiring repeated drainage (once per month or more frequent). An indwelling catheter (e.g., PleurX®) is allowed;

   d) Uncontrollable or symptomatic hypercalcemia (ionized calcium >1.5 mmol/L or calcium >12 mg/dL or corrected serum calcium > ULN);

e) History of malignant tumors, except esophageal cancer, within 5 years prior to randomization. However, patients with malignant tumors that have a negligible risk of metastasis or death (e.g., an expected 5-year survival rate >90%) and are expected to be cured after treatment can be enrolled, for example, an appropriately treated carcinoma in situ, basal or squamous cell skin cancer, local prostate cancer treated with by radical operation, and ductal carcinoma in situ treated by radical operation;

f) Palliative radiotherapy within 28 days prior to enrollment or radiopharmaceutical therapy within 8 weeks, except for localized palliative radiotherapy for metastatic bone lesions. The localized, palliative radiotherapy of a symptomatic lesion (such as bone metastasis or cancer invasion of nerves) shall be completed prior to enrollment/randomization and the patient has recovered from the side effects of such palliative radiotherapy. There is no minimum requirement for the period of time from recovery to enrollment/randomization.

g) Patients with bone metastasis of multiple vertebra that are prone to fractures and puts the patient at risk of paraplegia, except patients who are assessed by a specialist as stable and not in need of treatment;

h) Patients with advanced cancer with metastasis to vital organs and who are at risk of developing life-threatening complications in the short term (e.g., liver metastases involving >50% of total liver volume);

i) Patients with known complete obstruction under endoscopy who require interventions or surgery to remove the obstruction and have undergone tracheal or esophageal stenting;

j) Patients who have a body mass index of <17.5, a body weight decrease of >10% within 2 months prior to the first dose of the study treatment (considering changes of massive pleural effusion and ascites), or severe malnutrition displayed by other indicators.

2. General medical exclusion criteria:

a) Women who are pregnant, lactating, or plan to become pregnant during the study;

b) History of severe allergy, anaphylactoid, or other hypersensitive reactions to chimeric or humanized antibody or fusion protein;

c) Known allergy or hypersensitivity to the biological products manufactured from Chinese hamster ovary cells or any component of toripalimab;

d) History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid syndrome-related vascular thrombosis, Wegener's granulomatosis, Sjogren's syndrome, Guillain-Barre syndrome, multiple sclerosis, vasculitis, and glomerulonephritis;

- Patients with hypothyroidism but who receive stable-dose thyroid hormone replacement therapy can be enrolled in this study (refer to Appendix 6 for the replacement therapy for hypothyroidism);
- Patients with type I diabetes whose blood glucose can be controlled through stable-dose insulin can be enrolled in this study;
- Patients with eczema, psoriasis, chronic lichen simplex, or cutaneous manifestations only of vitiligo (e.g., patients with psoriatic arthritis will be excluded from the study) are allowed to be enrolled in this study if they meet the following conditions:
    - Rash must be <10% of body surface area (BSA);
    - The disease has been fully controlled at baseline, and only low-potency topical steroid therapy is needed;
    - No acute exacerbation of underlying diseases in the past 12 months (no need for psoralen plus ultraviolet A radiation, methotrexate, retinol, biological preparation, oral calcineurin inhibitor, or high-potency or oral steroid therapy).

e) History of idiopathic pulmonary fibrosis, organized pneumonia (e.g., obliterative bronchiolitis), drug-induced pneumonia, idiopathic pneumonia interstitial pneumonia, or evidence of active pneumonia found during chest CT screening scan;

f) Patients with a positive test result of human immunodeficiency virus (HIV);

g) Patients with hepatitis B virus (HBV) (known HBV surface antigen (HBsAg) and HBV DNA ≥1000 cps/mL or 200 IU/mL or ≥ULN at each study site) or hepatitis C virus (HCV):

- Patients with a previous HBV infection will be eligible to participate in this study only when their HBV DNA is negative (HBV DNA <1000 cps/mL or 200 IU/mL or < ULN);
- Patients with a positive HCV antibody can participate in this study only if they have negative polymerase chain reaction HCV ribonucleic acid (RNA).

h) Patients with active pulmonary tuberculosis (clinical diagnosis includes clinical history, physical examination, and radiological findings, as well as the tuberculosis test conducted in accordance with local medical routines);

i) Serious infection within 28 days prior to randomization, including but not limited to the infection complications, bacteremia, and severe pneumonia requiring hospitalization;

j) Oral or iv antibiotics within 2 weeks prior to randomization; patients receiving preventive antibiotic therapy (e.g., for prevention of urinary tract infection or prevention of exacerbation of chronic obstructive pulmonary disease) can be enrolled;

k) Important cardiovascular diseases, e.g., heart disease defined by the New York Heart Association (Grade 2 or above), myocardial infarction within 3 months prior to randomization, unstable arrhythmia, unstable angina pectoris, cerebrovascular accident, or transient cerebral ischemic attack. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must receive the treatment considered by the attending physician as the optimal treatment and may consult a cardiologist when necessary;

l) Major surgery (except for diagnostic operation) within 28 weeks prior to randomization or expected major surgery during the study;

m) Previous allogeneic bone marrow transplantation or solid organ transplantation;

n) Use of attenuated live vaccine within 28 days prior to randomization or plan to use such attenuated live vaccine during the study;

o) Any other disease, metabolic disorder, physical examination finding, or abnormal laboratory examination with the reason to suspect that it can lead to contraindicated

use of the investigational drug, affect reliability of the study results, or place the patient at high risk of treatment-related complications of diseases or conditions;

3. Exclusion criteria related to medications:

- Patients who have previously received any approved antitumor proprietary Chinese medicine within 2 weeks prior to the first dose of the study drug;
- Patients who have received treatments using other investigational products or participated in other clinical studies for therapeutic objectives within 28 days prior to randomization (including signing an ICF for other trials, and failure of screening);
- Previous immune checkpoint blocking therapy, for example, therapeutic antibodies of anti-PD-1 and anti-PD-L1 antibody;
- Previous systemic immunostimulatory therapy (including but not limited to IFN or interleukin-2) within 2 weeks or 5 $t_{1/2}$ prior to randomization, whichever last longer. Previous vaccinations with cancer vaccine are allowed;
- Use of systemic immunosuppressive drugs within 2 weeks prior to randomization, including but not limited to Prednisone (>10 mg/day or equivalent drug), Cyclophosphamide, azathioprine, methotrexate, thalidomide, and tumor necrosis factor (TNF);

  • Patients who have received short-term, low-dose, systemic immunosuppressant (e.g., 1 single dose of Dexamethasone for nausea) can participate in this study after discussion between investigators and the medical monitor and approval by the medical monitor;

  • Patients who use inhaled corticosteroids for treatment of chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for treatment of orthostatic hypotension and low-dose glucocorticoid (≤10 mg/d Prednisone or equivalent drug) supplement for treatment of hypoadrenocorticism are eligible.

- Patients receiving hematopoietic stimulating factors (e.g., granulocyte colony-stimulating factor [G-CSF] and erythropoietin) or blood transfusion within 2 weeks prior to randomization.

4. Exclusion criteria related to chemotherapy:

- History of allergy to cisplatin, carboplatin, or other platinum-based compounds;
- Grade 2 or higher peripheral neuropathy according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

4.1.3 Considerations for Other Inclusion Criteria

The investigator should refer to the Investigator's Brochure for details of warnings, precautions, contraindications, AEs, and other important data relating to the investigational drug to evaluate the impact of any potential safety factors on patient eligibility.

Following consultation with the Sponsor, rescreening is allowed under certain conditions. For example, if a patient's test result deviates slightly from the laboratory criteria and can be corrected and the result is not due to rapid worsening of disease or PD, then rescreening is allowed. Multiple attempts for rescreening are not allowed.

4.1.4 Additional Patient Requirements for Study Participation

Patients must also meet the following requirements for patients participating in the study:

- Ability to complete the protocol-specified visits in accordance with the requirements of the protocol;
- Agree to follow the restrictions for concomitant medications as described in Section 4.4.
- Female patients with childbearing potential agree to follow protocol-specified contraception measures beginning prior to enrollment through at least 60 days after the last dose of the study drug. Male patients agree to follow adequate contraception measures (complete abstinence or using condoms with spermicide) during the study through at least 60 days after the last dose of the study drug.
- For male patients who have partners with childbearing potential:

a) Unsterilized male patients who have partners with childbearing potential must use a male condom with spermicide beginning during from screening until at least 60 days after the last dose of study drug. Complete abstinence is an acceptable contraception method; however, occasional abstinence, safe period contraception (rhythm method), and coitus interruptus are not acceptable.

b) The female partner (of childbearing potential) of a male patient must also adopt highly effective contraception measures in this period (the same requirements for female patients).

- Strenuous exercise should be avoided for 72 h prior to the scheduled study visits.

4.2 Treatment Allocation and Blinding

After obtaining the patient's signed ICF and determination of their inclusion eligibility, the research site will input patient demographic and baseline characteristics via the interactive voice/web response system (IxRS). For patients who meet the criteria, the research site will obtain the patients' randomization number and assigned treatment group via the IxRS.

The enrolled patients will be randomized in a 1:1 ratio to one of the treatment groups (toripalimab or placebo with paclitaxel and cisplatin). Permuted block randomization will be adopted to ensure balanced assignment between the treatment groups. Randomized patients will be stratified by the following conditions:

- ECOG performance status score (0 or 1)
- Prior radiotherapy (yes or no)

Patients shall receive the first dose of the investigational drug on the date of randomization if possible. If not feasible, the first dose of the investigational drug should be administered within 3 calendar days after randomization.

To maintain the study blind for treatment assignment, blood samples for ADA and trough concentration must be collected from the patients in the control group; however, the measured results for ADA/trough concentration are generally not required for patient safety or to interpret the trial results. The relevant Sponsor staff or the designee responsible for determination of ADA/trough concentration may obtain access to patient treatment assignments (for details, see the Maintenance of Study Blinding Plan), to determine appropriate ADA/trough concentration samples for analysis. Unless required explicitly (e.g., for evaluation of possible administration error), the ADA and toripalimab concentration samples for patients in the control group will not be analyzed.

Unblinding of treatment assignment will be conducted via IxRS. It is strongly suggested that the investigator should not unblind information for individual patients. If unblinding is required for patients' management (e.g., in the event of an SAE, the information of treatment

assignment would possibly influence the treatment measures for the patient), the investigator may unblind via IxRS. Unblinding is not allowed for non-emergencies. If an investigator desires to know the information of the investigational drug for any other reason, the investigator should contact the medical monitor directly.

The investigator should record and provide the reasons (e.g., accidental unblinding or unblinding for evaluation of an SAE) for premature unblinding. If a research site unblinds the information inappropriately, the research site may be required to withdraw from the study.

If unblinding to patients and/or investigator occurs during the study, the Sponsor must be notified immediately. The information for unblinding a patient's treatment code must be recorded in the patient's source documents (medical records) and in the randomization (IxRS) system.

For regulatory reporting purposes, if a local health authority requires it, the Sponsor will unblind the treatment code for all unexpected, suspected serious adverse reactions (refer to Section 5.7) as considered by the investigator or the Sponsor.

At end of the study, all patients still receiving the therapy will be unblinded. Only the patients randomized into the toripalimab arm may continue the treatment with toripalimab. The patients in the placebo arm are not allowed to be crossed over to toripalimab arm.

4.3 Treatment Plan

4.3.1 Formulation, Packaging and Disposal

4.3.1.1 Study Drug

Toripalimab is a recombinant humanized antihuman PD-1 IgG4 kappa monoclonal antibody. Toripalimab contains a complementary determinant region of murine antibody that may bind to human PD-1, as well as a human framework region with limited reverse mutations in the parental murine sequence. Introduction of a serine to proline at protein site 228 minimizes Fab arm exchange. Toripalimab is produced by recombinant DNA technology using the Chinese Hamster Ovary Mammalian Cell Expression System (LONZA). The predicted molecular weight of toripalimab is approximately 147 kDa, and it consists of 2 heavy chains of 452 amino acids, and 2 light chains of 219 amino acids. Toripalimab has a N-linked glycosylation site at Site 302 of the heavy chain. The isoelectric point of toripalimab is 6.4 to 7.4. The drug product of toripalimab is an aseptic liquid of 6 mL, supplied in a glass bottle

(Fluorotech stopper and aluminum-plastic composite lid) and administered via iv infusion. Refer to Table 3 for the description of the drug product of toripalimab and placebo; The study drug should be stored at 2°C to 8°C and protected from light.

Table 3 Chemistry and Manufacturing Information for Toripalimab and Placebo

Investigational drug/control drug	MFR.	Supplied concentration and formulation
Toripalimab	Suzhou Zhonghe Biosciences Co., Ltd. Longqiao Roads No. 999, Suzhou City, Jiangsu Province, China; postal code 215200	Sterile liquid containing toripalimab 240 mg. The nominal concentration is 40 mg/mL, containing 20 mM sodium citrate, 2.5% (w/v) mannitol, 50 mM NaCl, and 0.02% (w/v) polysorbate 80. pH value is 6.0. Each bottle contains 6 mL of effective volume.
Placebo	Suzhou Zhonghe Biosciences Co., Ltd. Longqiao Roads No. 999, Suzhou City, Jiangsu Province, China; postal code 215200	Sterile liquid containing 20 mM sodium citrate, 2.5% (w/v) mannitol, 50 mM NaCl, and 0.02% (w/v) polysorbate 80. pH value is 6.0. Each bottle contains 6 mL of effective volume.

The sterile liquid of toripalimab or placebo is supplied in a 6-mL glass vial (Westar® stopper and aluminum-plastic composite lid), and is provided to the research site by a separate drug box for multiple patients with 1 vial in each drug box. A white label is attached to the drug box and vial of toripalimab or placebo. Other codes are not used.

The main label on the vial contains the following information: protocol number, content of toripalimab or placebo, batch number, expiration date, storage conditions, and instructions for use. The content of the label is in accordance with Good Manufacturing Practice (GMP) and local regulatory requirements. Label text must be translated into the local language, if applicable.

Toripalimab/placebo is provided by the Sponsor.

4.3.1.2 Chemotherapeutic Drugs

In the study, the chemotherapeutic drugs are paclitaxel and cisplatin. The marketed dosage form of each drug is provided by the Sponsor. Please refer to the corresponding package inserts for details regarding the strength, packaging, storage and handling information of paclitaxel and cisplatin. Please refer to the package insert for a detailed description of preparation for administration of paclitaxel and cisplatin.

4.3.2 Study Treatment Dosages, Administration and Compliance

The study will include an induction period and a maintenance period. Patients will receive toripalimab or placebo combined with a TP regimen for combined therapy in the induction period in 1 treatment cycle of 3 weeks, and for up to 6 cycles, on Day 1 of each cycle. The patients will then enter the maintenance period of toripalimab or placebo monotherapy, which will be administered on Day 1 of each cycle (1 treatment cycle consisting of 3 weeks) until intolerable toxicity, PD, patient refusal to continue study drug treatment, judgment by investigator that the patient needs to be withdrawn from the treatment, or up to two years of treatment, whichever occurs first. The protocol allows an excursion of up to ±5% for each dose of paclitaxel or cisplatin.

4.3.2.1 Administration of Study Drugs

The study drug may be either toripalimab or placebo. The eligible patients will be randomized to toripalimab or placebo in combination with TP chemotherapy.

Toripalimab 240 mg/placebo will be administered on Day 1 of each 3-week cycle (Q3W) via iv infusion in a monitored environment. The environment will be equipped with specialized staff and adequate devices/drugs to manage any possible serious allergic reactions occurring in patients at any time (See Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST)).

The dose of toripalimab 240 mg/placebo will be diluted in an infusion bag containing 100 mL of 0.9% NaCl and administered via iv infusion over ≥ 60 minutes, followed by an observation period of 60 min (required in the first 2 cycles only). If no clinically significant, infusion-related adverse reactions occur in the first 2 cycles, then the study drug may be infused over 30 (±10) minutes in subsequent cycles.

The infusion of toripalimab will follow the instructions as shown in Table 4.

Table 4 Administration Procedures for First and Subsequent Infusions of Study Drug

First infusion	Subsequent infusions
• Premedication is not allowed. • Within 60 min prior to infusion, the patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) shall be recorded. • Toripalimab/placebo is infused for ≥60 min.	• If a patient develops infusion-related reactions in the previous infusion, the physician may decide, at his/her discretion, to treat the patient with antihistamine in cycle 2 and in subsequent cycles thereafter.

First infusion	Subsequent infusions
• At 30 (±10) min after infusion, the patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) shall be monitored. At 60 (±10) min after infusion, the patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) shall be recorded. • Patients will be informed of any delayed symptoms that may occur after infusion and that they should contact the study physician if such symptoms occur.	• At 60 (±10) min after the second infusion, the patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) shall be recorded. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded during the infusion if indicated clinically or if a patient develops symptoms in the previous infusion. • If no infusion-related adverse reactions occur in the first 2 infusions, the subsequent administration is allowed to be completed in 30 (±10) min, and the 60-min observation period may be exempted. • If infusion reactions occur in the previous infusions, subsequent toripalimab iv infusion time must be at least 60 min. • If infusion reactions or clinical indications occur in the prior infusion, the patient's vital signs must also be monitored for 60 min (±10 min) after infusion.

Dose adjustment of the study drug is not allowed. Please see Section 5.1.5.2 for dose modifications of study drug due to an AE and management of toripalimab-specific AEs.

4.3.2.2 Administration of Chemotherapy

Initiation of administration of the chemotherapeutic drugs begins 1 h after the end of infusion of the study drug in the first 2 cycles, if and vital signs are normal and stable. The chemotherapeutic drugs are infused in the order of first paclitaxel and then cisplatin. See Table 5 for the details of the administration of the TP regimen. Chemotherapy must be administered as described in Table 5. If the administration of chemotherapy as specified in the protocol is significantly different from the procedures at the research site, please contact the medical monitor.

Table 5 Dosage Regimens of Paclitaxel and Cisplatin

Chemotherapeutic drugs	Dose/route of administration	Induction period (up to 6 cycles)	Maintenance period
Paclitaxel	175 mg/m^2, iv infusion	iv infusion, over 3 h or per local clinical practices, on Day 1 of each cycle (Q3W)	NA
Cisplatin	75 mg/m^2, iv infusion	iv infusion at a rate of approximately 1 mg/min or per local clinical practices on Day 1 of each cycle (Q3W)	NA

NA = not applicable

When patients receive TP chemotherapy, they should receive prophylactic treatment against hypersensitivity reactions or vomiting and also receive adequate hydration prior to chemotherapy administration. See Section 4.3.4.1 for details of the prophylactic regimen for TP.

Please see Section 5.1.5.3 for dose adjustment of paclitaxel and of cisplatin during the study.

The computational equation for BSA[45] is:

BSA (m^2) = SQRT ([height (cm) × body (kg)]/3600)

Note: SQRT = square root

4.3.2.3 Medication Compliance

The dose and time of administration of the investigational drug and chemotherapeutic drugs for each patient in each treatment cycle shall be recorded in the eCRF. The reasons for delayed administration, dose adjustment, or missing administration should also be recorded in eCRF.

4.3.3 Storage, Handling and Retention of the Study Drugs and Chemotherapeutic Drugs

All unused investigational drugs will be stored in the designated storage place at the research site according to the specified storage conditions (2°C to 8°C, protected from light). The Sponsor shall regularly arrange a third party to recover empty vials of used investigational drugs. If the study drug is lost or the packaging is damaged, the detailed situation should be recorded.

In the study, the chemotherapeutic drugs include paclitaxel and cisplatin. Please refer to the corresponding package insert for the strength, packaging information, and disposal method of the chemotherapeutic drugs. The study drug is toripalimab alongside placebo. Paclitaxel and cisplatin are non-study drug. All study drugs (toripalimab/placebo) and non-study drugs (paclitaxel and cisplatin) required for the study will be provided by the Sponsor.

The research site will confirm receipt of study drug via IxRS and confirm shipment conditions and contents; non-study drug will be managed manually. If the study drug is damaged, it will be replaced.

The study drug will be disposed of at the site according to the site's in-house standard operating procedures (SOPs) or returned to the Sponsor, which will be appropriately recorded. The research site must obtain written permission from the sponsor before study drug destruction; study drug destruction must be recorded on the appropriate tracking document.

The receipt, distribution, return, and destruction of all study drug and non-study drug at the research site should be accurately recorded on the Drug Inventory Log.

4.3.4 Prophylactic Medications

Prophylactic drugs should be given prior to administration of paclitaxel and cisplatin to prevent potential allergic reactions and vomiting. The patients must also receive adequate hydration prior to administration of chemotherapy. See Table 6 for the recommended prophylactic regimen for chemotherapy or refer to local clinical practices.

Table 6 Prophylactic Regimens Administered Prior to Paclitaxel and Cisplatin Administration

Pretreatment medications	Dose/route of administration	Time of dosing
Prophylaxis for allergic reaction		
Dexamethasone	20 mg, orally	Dexamethasone 20 mg, orally, 12 and 6 h prior to administration of Paclitaxel
Diphenhydramine (or another drug in this class)	50 mg, iv infusion	Diphenhydramine 50 mg (or a drug of the same kind) within 60 min prior to administration of Paclitaxel
Histamine 2 receptor antagonist (cimetidine or ranitidine)	Cimetidine 300 mg or Ranitidine 50 mg, iv infusion	Histamine 2 receptor antagonist (Cimetidine 300 mg or Ranitidine 50 mg) within 60 min prior to administration of Paclitaxel.
Hydration		
0.9% sodium chloride	500-1000 mL, iv infusion	500-1000 mL of 0.9% sodium chloride solution is first given prior to administration of Cisplatin, and 1000-2000 mL of the solution is given after administration.
Mannitol and furosemide	Oral or iv	Mannitol and furosemide (Lasix) may be used supportively before and after hydration.
Anti-emetic Prophylaxis		
5-HT3 antagonist (e.g., Ondansetron)	In accordance with the package insert	It is suggested that the research sites adopt 5-HT3 antagonist (e.g., Ondansetron) for the prevention of vomiting prior to the start of chemotherapy.

4.3.5 Access to Toripalimab After Study Closure

After the completion of 2 years of treatment, toripalimab will be provided free of charge to patients in the toripalimab arm who meet **all** the criteria below.

- Disease progression occurs after discontinuation of toripalimab.
- The investigator judges that the patient may benefit from re-treatment with toripalimab.
- The patient requires continued use of toripalimab for his or her well-being.
- There is no alternative anti-cancer therapy.
- The patient and his or her doctor comply with the corresponding legal or regulatory requirements.

After completion of the study, patients will not receive toripalimab provided by the Sponsor for free under any of the following circumstances:

- The investigational drug is commercially available and affordable in the country where the patient lives (e.g., it is covered by the patient's insurance, or it does not result in economic difficulties for the patient).
- The Sponsor has stopped development of toripalimab or the data have demonstrated that toripalimab is ineffective on relapsed or metastatic esophageal cancer.
- The Sponsor has safety concerns regarding use of toripalimab in the treatment of advanced or metastatic esophageal cancer.

4.4 Concomitant Medication and Concurrent Therapy

Concomitant medications include all drugs/concomitant therapies taken by the patient from 28 days prior to enrollment to the end-of-treatment visit. Any medications taken during the study by the patient must be approved by the investigator and used under the direction of the investigator.

- Oral contraceptive;
- Hormone replacement therapy;
- Prophylactic or therapeutic anticoagulation (e.g., a stable dose level of low molecular weight heparin or warfarin);
- Patients may receive localized, palliative radiotherapy (e.g., for treatment of known bone metastases) if the irradiated lesion is not the only site of disease and it does not interfere with the evaluation of tumor response in accordance with RECIST 1.1, so that tumor response in patients may still be evaluated;
- Inactivated influenza vaccine (only to be administered during influenza season);
- Megestrol for appetite stimulation;
- Inhaled corticosteroids for treatment of chronic obstructive lung disease;
- Mineralocorticoids (e.g., fludrocortisone) as hormone replacement therapy;
- Low-dose corticosteroids for orthostatic hypotension or adrenocortical insufficiency;
- Bisphosphonate for treatment of bone metastasis.

Generally, the investigator should treat the patient with supportive therapy in accordance with local standards and based on clinical indications. Patients with infusion-related reactions are treated with acetaminophen, Ibuprofen, diphenhydramine, and/or famotidine or other H2-receptor antagonists in accordance with the standard medical practices. Patients with serious infusion reactions such as dyspnea, hypotension, wheezing, bronchospasm, tachycardia, decreased oxygen saturation, or respiratory distress should receive additional medical interventions appropriate for the type and severity of symptoms.

Patients with local bone metastasis are allowed to receive localized radiotherapy prior to the first dose of study drug to control symptoms (e.g., palliative therapy for bone metastatic lesion). At enrollment, patients must have completed such therapy and recovered from all prior therapy-related toxicities. During treatment, palliative therapy for known bone metastatic lesion is permitted as long as it does not interfere with evaluation of any tumor target lesion (e.g., the lesion to be irradiated is not the only target lesion) in accordance with RECIST 1.1. Toripalimab treatment can be continued during palliative therapy.

All concomitant medications and concomitant therapies must be recorded in the Concomitant Medications page of the eCRF.

4.5 Prohibited Therapy

Unless otherwise indicated, the following drugs are prohibited when patients are receiving the investigational therapy:

- Other tumor-related radiotherapies, chemotherapies, immunotherapies, or hormone therapies (except antiallergic drugs), as well as other investigational drugs;
- Approved traditional Chinese drug products for treatment of cancer; refer to the relevant classification and regulations specified in the Expert Consensus on Use of Palliative Chinese Patent Medicine in Oncology.
- Any attenuated live vaccines are prohibited within 28 days prior to randomization and during treatment.
- Prophylactic G-CSF is not permitted within the first 2 weeks prior to the first cycle. Thereafter, symptomatic or prophylactic therapy should be given in accordance with the guidelines or local clinical practices.

If a patient requires any other specific anticancer therapy as judged by the investigator, then the patient should terminate treatment of the investigational drug prematurely prior to receiving a new anticancer therapy.

4.6 Study Assessments

See Appendix 1 Schedule of Assessments for the schedule of study visits and assessments for this study Flow Sheet.

All patients will be closely monitored for safety and tolerability of treatment throughout the study. Each patient must undergo all required assessments and the results will be recorded in the eCRF.

Prior to treatment on Day 1 of each cycle, the investigator will evaluate the patient for eligibility. The study drug and the chemotherapy may be administered only if the clinical evaluation of the patient and laboratory test results are within acceptable ranges.

4.6.1 Informed Consent Form and Screening Evaluation

A written ICF for this study, signed by the patient, must be obtained prior to any study screening examination or evaluation, within 28 days prior to start of the investigational therapy. ICFs for all unenrolled and enrolled patients will be stored at the research site.

All screening evaluations must be completed and the results must be reviewed to confirm that the patient meets all the inclusion criteria prior to randomization. The investigator will record the information of all screened patients in the screening log and, if applicable, confirm the patient's eligibility or record the reason for screening failure.

For patients who develop PD on study and in whom the investigator has determined that the potential for clinical benefit exists, may continue to receive study drug (blinded) only after they agree to undergo a biopsy of the progressing lesion (if clinically feasible) and sign an ICF acknowledging the risks of the delay of administration of other therapeutic regimens.

4.6.2 Demographic Information and Baseline Disease Characteristics

Medical history to be collected includes clinically significant diseases, surgery, non-esophageal cancer (including prior antitumor therapies and surgeries), fertility status, smoking history, alcohol consumption, and drug abuse.

History of esophageal cancer includes prior antitumor therapies and surgeries for cancer.

Demographic data will include age, sex, and self-reported ethnicity.

4.6.3 Physical Examination

The patients will undergo physical examinations at the specified timepoints in Appendix 1 Schedule of Assessments, Study Flow Sheet; see Appendix 1 Schedule of Assessments for the specific examination items. Any abnormality at baseline should be recorded in the eCRF for General History and Baseline Diseases.

Symptom-oriented physical examination will be conducted in subsequent visits (and as clinically indicated). Any new or worsening, clinically significant physical finding or abnormality should be recorded in the eCRF as an AE.

4.6.4 Vital Signs

Patients will be assessed for vital signs at the timepoints specified in Appendix 1 Schedule of Assessments, Study Flow Sheet; the assessed items include temperature, pulse rate, respiratory rate, and blood pressure. Baseline abnormalities are recorded in eCRF for General

History and Baseline Diseases. In subsequent visits, any new or aggravated, clinically significant abnormality should be recorded in the CRF for Adverse Events.

4.6.5 Electrocardiogram

Patients will undergo a 12-lead ECG at the timepoints specified in Appendix 1 Schedule of Assessments, Study Flow Sheet. During the study, every effort shall be made to ensure that the same machine be used for obtaining the patient's ECG. The position of leads should be consistent as far as possible. The ECG must be conducted after the patient has rested in the supine position for at least 10 minutes.

To monitor safety, the investigator must review, sign, and date all ECGs. The paper copy of electrocardiogram will be retained in the permanent study file at the research site. Any change in the waveform morphology or other ECG abnormalities must be recorded in the appropriate eCRF.

4.6.6 Echocardiography

During the study, the patients undergo an echocardiogram to measure left ventricular ejection fraction at the timepoints specified in Appendix 1 Schedule of Assessments, Study Flow Sheet.

4.6.7 ECOG Performance Status Score

During the study, the patients will be assigned an ECOG performance status score at the timepoints specified in Appendix 1Schedule of Assessments, Study Flow Sheet; see Appendix 9 for the scoring criteria.

4.6.8 Laboratory Tests

During the study, the following laboratory tests will be conducted at the timepoints specified in Appendix 1 Schedule of Assessments, Study Flow Sheet. The samples used for the laboratory tests must be sent to the local laboratory of the research site, and the laboratory tests in the treatment period should be completed prior to administration of each dose. The investigational drug will not be administered until the laboratory test results meet the criteria for continued medication as judged by the investigator. The detailed test items are provided below (for details, see Appendix 1 Schedule of Assessments, Study Flow Sheet):

- Hematology (complete blood cell count, including red blood cell count, hemoglobin, hematocrit, white blood cell count and differentials [neutrophils, eosinophils, lymphocytes, monocytes, and basophils], and platelet count);
- Blood biochemistry (glucose, blood urea nitrogen or urea, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, total bilirubin, direct bilirubin, ALT, AST, ALP, lactate dehydrogenase (LDH), total protein and albumin, serum creatine kinase, and serum creatine kinase isoenzymes);
- Coagulation (INR, PT, aPTT);
- A serum pregnancy test will be conducted only for female patients of childbearing potential in the screening period, including those who have undergone bilateral tubal ligation.
- A female patient of childbearing potential is defined as the one who is not surgical sterilized (e.g., hysterectomy, and/or bilateral oophorectomy), or is not postmenopausal (amenorrhea ≥1 year);
- Urinalysis (urine pH, specific gravity, glucose, protein, ketone bodies, occult blood, red blood cells, and white blood cells);
- Thyroid function tests (TSH, free T3, and free total thyroxine);
- HBV serology (HBsAg, anti-HbsAg antibody, and hepatitis B core antibody [anti-HBc]);
- If the patients are HbsAg positive or have a prior history of hepatitis B infection, then an HBV DNA test should be conducted prior to randomization;
- HCV serology (anti-HCV antibody);
- HIV test: All patients must receive an HIV test prior to enrollment into the study, and those who are positive for HIV are not eligible for enrollment into the study.

4.6.9 Analysis of Biological Specimens

4.6.9.1 Anti-drug Antibody Test

Patients may develop an immune response to toripalimab, that is, an anti-drug antibody (ADA) response. During the study, at the timepoints specified in Appendix 2, blood will be collected and analyzed using a sensitive validated screening method to test for ADA in serum

samples. Patients who develop signs or adverse events possibly due to ADA shall be monitored closely.

4.6.9.2 Biomarker Analysis

During the study, blood samples will be collected from all enrolled patients at the timepoints specified in Appendix 2 to test for biomarkers (including but not limited to PBMC, PD-L1, MSI, 11q13, tumor mutation burden, and others). To measure changes in certain blood biomarkers (e.g., for circulating tumor DNA [ctDNA]), the samples are processed to separate plasma or serum. Whole blood samples will be processed to assess RNA and DNA and to evaluate immune-related biomarkers, cancer type-specific biomarkers and other exploratory biomarkers (e.g., change in gene expression or single-nucleotide polymorphism).

Any remaining samples collected for the analysis of biomarkers and ADA may be used for further analysis of exploratory biomarkers, pharmacodynamic analysis, and other safety assessments. Any residual patient samples for biomarker and ADA analysis will be stored in the central laboratory until the approval certificate by NMPA is obtained, at which point they will be destroyed by the central laboratory.

4.6.10 Tumor Assessments

Tumor status will be evaluated in accordance with RECIST version 1.1 and irRECIST. Baseline tumor evaluation in patients must be conducted within 28 days prior to enrollment by contrast-enhanced CT or MRI scans of the neck, chest, abdomen, and pelvis. Tumor imaging results conducted at the research site within 28 days prior to enrollment into the study can be accepted as baseline assessments. Baseline and subsequent imaging should be conducted by the same imaging method (CT or MRI) and evaluated by the same reader, if possible. At screening, a contrast-enhanced brain CT or MRI scan is to be conducted in all patients to evaluate for the presence of CNS metastases. If CT scan results are inconclusive, then a brain MRI scan must be conducted to evaluated for CNS metastases. Patients with active or untreated CNS metastasis are not eligible to participate in the study. At screening, patients with symptoms of bone metastases, a history of bone metastasis, or suspected bone metastasis at baseline must undergo a bone scan (those who undergo a bone scan within 60 days prior to enrollment do not require another one at baseline). If indicated clinically, an appropriate method can be used to examine other known or suspected lesions; radiological

examinations conducted for routine evaluation of tumor do not need to be repeated if they are done at the same study site and are within 28 days prior to enrollment.

The patient will undergo a tumor evaluation at baseline (screening period) and every 6 weeks (±7 days), regardless of dosing delays, for the first 12 months after the start of treatment. After the first 12 months, tumor evaluations should be performed every 9 weeks (±7 days), regardless of dosing delays, until intolerable toxicity, PD, patient refusal to continue study drug treatment, judgment by investigator that the patient needs to be withdrawn from treatment, or up to two years of treatment, whichever occurs first. For patients who continue treatment beyond RECIST 1.1-defined PD, treatment will be continued until intolerable toxicity, confirmed disease progression on a second assessment per irRECIST, patient refusal to continue study drug treatment, judgment by investigator that the patient needs to be withdrawn from the treatment, or up to two years of treatment, whichever occurs first.

For patients who terminate the treatment for any reason other than PD (e.g., toxicity), tumor evaluation must be conducted every 6 weeks (±7 days) for the first 12 months and thereafter every 9 weeks (±7 days) until PD, loss of clinical benefit, death, withdrawal of informed consent, start of a new antitumor therapy, lost to follow-up, termination of study by the Sponsor, whichever occurs first.

Patients who continue study drug after PD in accordance with RECIST 1.1 and choose to remain on blinded study treatment will undergo tumor evaluation assessments according to the above schedule.

Patients who are suspected to have PD prior to the next scheduled tumor evaluation should undergo an unscheduled tumor evaluation.

If a patient withdraws from study treatment for any reason, an imaging examination must be conducted at the end-of-treatment visit, unless the previous imaging examination is within 28 days of withdrawal from the study.

The mode of scan should be the same as baseline, including scanning layer thickness and contrast medium.

All images, including CT or MRI scan, will be collected and retained by the Sponsor for potential future evaluation by BICR in accordance with RECIST 1.1. The decision to conduct an independent review of radiologic images will be made prior to the analysis of the primary efficacy endpoint.

4.6.11 Tumor Tissue Samples

4.6.11.1 Tumor Tissue Samples Archived and Freshly Collected for Screening

At screening, tumor specimen paraffin blocks (preferred) or at least 8 unstained consecutive tissue slices of formalin-fixed paraffin embedded tumor specimens must be submitted. The pathology reports for the above specimens must also be provided, to determine PD-L1 status, as well as expression information for microsatellite instability (MSI), 11q13 amplification, and tumor mutation burden.

Tumor samples must be of good quality in terms of tumor content (if the submitted tumor samples are not sufficient to determine PD-L1 expression, then the research site will be notified for re-cut or supplement).

If there is no archival tumor tissue sample is available for submission, patients must consent to and undergo a tumor biopsy during the screening in order to be enrolled in the study.

The acceptable biopsy specimens include excisional biopsy, core needle biopsy, incisional biopsy, and endoscopic biopsy. Patients with less than 8 unstained consecutive tissue slides of FFPE tumor specimens at baseline may participate in the study as agreed by investigators following discussion with the medical monitor.

Unacceptable samples include the following:

- Fine needle aspiration sample, brush biopsy sample, and cell mass sample (e.g., hydrothorax cell precipitation sample and lavage sample);
- Tumor tissues from bone metastasis.

4.6.11.2 Collection of Tumor Samples at Radiologically Confirmed PD

Unless clinically infeasible, it is suggested that tumor biopsy be performed in all patients with PD.

The acceptable biopsy specimens include excisional biopsy, core needle biopsy, incisional biopsy, and endoscopic biopsy. Tumor samples may be evaluated for immune—related and tumor type-related characteristics, as well as other exploratory biomarkers (including but not limited to PBMC, PD-L1, MSI, 11q13, tumor mutation burden, and others).

4.6.11.3 Collection of Tumor Samples at Other Timepoints

During the study, if a patient requires any surgery or procedures (e.g., bronchoscopy, esophago-gastroduodenoscopy, and colonoscopy) to possibly obtain tumor tissue, then remaining samples or partial samples (remaining tumor tissues) for medical diagnosis should be collected for exploratory analysis. Acquisition of the tissue samples collected at different timepoints from patients may help better understand the dynamic expression of biomarkers and their relationship with antitumor therapy.

4.6.11.4 Use and Storage of Remaining Samples in the Relevant Procedures of the Study

The remaining samples obtained from the relevant procedures of the study will be destroyed within 5 years after the end of the study or destroyed earlier in accordance with local laws and regulations. If patients agree to storage of tumor samples at Shanghai Junshi Biosciences, Co., Ltd., for further study, then the samples may be stored in the central laboratory until the approval certificate by NMPA is obtained, at which point they can be destroyed by the central laboratory.

4.6.12 Patient-reported Outcomes

EORTC QLQ-C30 and QLQ-OES18 questionnaires will be used to collect patient-reported outcome (PRO) data to determine the clinical characteristics of toripalimab (see Appendices 7 and 8).

The questionnaires are translated into local language as required. To ensure collection data that is valid and complies with the requirements by the health regulatory authorities, the questionnaires should be completed independently during each on-site visit by the patient, prior to the conduct of other non-PRO evaluations and administration of study treatment.

4.6.13 Schedule of Assessment

4.6.13.1 Screening and Baseline Assessments

The screening test and evaluation will be conducted within 28 days prior to Cycle 1 Day 1. The tumor imaging examination results of patients, conducted at the research site within 28 days prior to enrollment into the study, are acceptable.

See Appendix 1 Schedule of Assessments, Study Flow Sheet, for the schedule for screening assessments, and Appendix 2 for the collection timepoints of ADA and biomarkers samples.

4.6.13.2 Assessments During Treatment

All treatment visits must be completed within the scheduled dates (±3 days), unless otherwise noted (see Appendix 1 Schedule of Assessments, Study Flow Sheet). Unless otherwise indicated, the scheduled assessment must be completed by Day 1 of each cycle, prior to administration of study treatment.

If administration of the study treatment and the study assessments are not conducted as scheduled, i.e., due to holidays, weekends, or other events, then the study drug/study treatment should be administered as soon as feasible. Upon resumption, if the delay in administration of study treatment is no more than 3 days, the next dose will be administered according to the original schedule. If study treatment is delayed more than 3 days but less than 56 days, study treatment will be administered every 21 days from resumption of treatment.

See Appendix 1, Study Flow Sheet, for the assessment schedule for the study and Appendix 2 for the collection timepoints for ADA and biomarkers samples.

4.6.13.3 Assessments at the End-of-treatment Visit

Patients are required to return to the research site for the end-of-treatment visit within 30 days after discontinuation of study drug treatment, regardless of the reason for the discontinuation of study treatment. If the decision to discontinue the treatment is made at a treatment visit, this treatment visit can serve as the end-of-treatment visit. If more than 30 days elapse between the decision to discontinue treatment and the end-of-treatment visit, the investigator should complete the end-of-treatment visit as soon as possible.

After the end-of-treatment visit, patients will be followed for survival according to the follow-up assessment schedule and special laboratory assessment schedule, please see the Appendix 1 Schedule of Assessments, Study Flow Sheet and Appendix 2.

4.6.13.4 Follow-up Assessments

After end-of-treatment visits, follow-up should be conducted as described in Section 5.5, if they have unresolved AEs or begin survival follow-up telephone and/or clinic visit every month (±7 days) until death, withdrawal of consent to continue on study, loss to follow-up, or termination of the study by the Sponsor.

Follow-up will include collection of information on subsequent antitumor therapies and survival status.

Please see Appendix 1 Schedule of Assessments, Study Flow Sheet, and Appendix 2 for the survival follow-up assessment schedule.

4.6.13.5 Assessments at Unscheduled Visits

Unscheduled visits should be conducted as clinically indicated, based on new or worsening AEs, intercurrent illness, or to evaluate for possible disease progression. The data obtained during an unscheduled visit should be recorded on the Unscheduled Visits page in the eCRF.

4.7 Discontinuation of Study Treatment

4.7.1 Discontinuation of Study Treatment By Patients

Patients may withdraw voluntarily from the study for any reason. The reasons for withdrawal from the study include but are not limited to the following items:

- Withdrawal of consent to continue study treatment or protocol-required procedures;

Information on patients who withdraw from the study should be obtained, if possible. The primary reason for withdrawal from the study should be recorded in the corresponding eCRF. However, if a patient withdraws consent for to remain on study and complete study visits, the patient will not be followed up after withdrawal of such consent. Any patient who withdraws consent to remain on the study will not be replaced.

The investigator should ask the patient why they wish to withdraw from the study and request that the patient return to the research site for an end-of-treatment visit, if possible. If the patient is unable to return for the scheduled visit, the investigator should do everything possible to ensure the patient returns to the research site to complete the end-of-treatment visit as soon as they can.

4.7.2 Discontinuation of Study Treatment by Investigators

Discontinuation of Study Drug

The investigator has the right to discontinue treatment or to withdraw a patient from the study. The study drug must be terminated for any of the following:

- PD on imaging according to RECIST 1.1 and the patient does not wish to continue study treatment or the investigator determines that the benefit-risk assessment for continued treatment is not favorable after comprehensive evaluation of imaging data, tissue biopsy results and clinical condition.
- The patient develops intolerable treatment-related AEs, including intolerable immune-mediated AEs as determined by the investigator.
- Any new or worsening medical condition under which continuation of the study drug might be detrimental to the patient's safety.
- The patient has received another antitumor therapy not specified in the protocol.
- Non-compliance of the patient with the protocol.
- Pregnancy.

Exceptions: A patient with PD per RECIST 1.1 may continue treatment with study drug if, as judged by the Sponsor and the treating doctor, that all of the following criteria are met:

- Evidence of clinical benefit, as evaluated by the investigator;
- No symptoms or signs indicative of life-threatening risks due to PD (including worsening laboratory test results, e.g., new or aggravated hypercalcemia);
- No decrease in ECOG performance status score due to PD;
- There is no tumor progression at important anatomical sites (e.g., leptomeningeal disease) that present life-threatening risks or morbidity; no progression at disease sites requiring medical interventions that are prohibited by the protocol; and the patient is clinically stable;
- At the first documentation of PD, if a patient chooses to remain on study treatment, the patient must sign an ICF acknowledging that such treatment will delay standard therapy and agreeing to continue treatment with toripalimab/placebo.

In accordance with RECIST 1.1, a patient who develops a further PD on a second assessment must permanently terminate study drug treatment.

Discontinuation of chemotherapy

A patient who develops PD in accordance with RECIST 1.1, must terminate chemotherapy without exception.

The primary reason for termination of the study treatment or withdrawal of a patient from study should be recorded in the corresponding eCRF.

4.7.3 Termination of the Study and/or Closure of the Research Site

The Sponsor has the right to terminate the study at any time. The reasons for study termination may include but are not limited to the following:

- The incidence and severity of AEs in this or other studies suggest study drug poses a potential health hazard to patients.
- The rate of enrollment of patients is unsatisfactory (slow accrual rate).

If the Sponsor decides to terminate the study, investigators will be notified.

The Sponsor has the right at any time to close a research site at any time. The reasons for closure of a research site may include but are not limited to the following:

- Very slow accrual;
- Poor compliance with the trial protocol;
- Inaccurate or incomplete data records;
- Non-compliance with the International Conference on Harmonisation (ICH) GCP guidelines;
- Study-related activities are no longer being conducted (i.e., all patients have completed the study, and all responsibilities have been performed).

5 Safety Evaluation

Toripalimab is marketed in China for the treatment of unresectable or metastatic melanoma after failure of prior systemic therapy. The use of toripalimab for esophageal cancer is still in the clinical development stage. Currently, the clinical experience of toripalimab in humans is limited, and the full safety profile is still not fully evaluated. The following information is based on non-clinical and clinical findings, as well as published data of similar drugs.

5.1 Safety Plan

Various measures will be taken to ensure patient safety while participating in this study, including use of strict inclusion and exclusion criteria (see Section 4.1.1 and 4.1.2) and close monitoring (see the text below and Section 4.6). Please see Section 5.3 for the complete and detailed content of the safety report in this study (method, date, and time of collection of safety parameters; evaluation of safety information).

The study drug will be administered in a setting that has emergency medical equipment and staff trained in monitoring and management of medical emergencies.

During the study, all AEs and SAEs shall be recorded until 60 days after the last dose of study drug or initiation of a new antitumor therapy, whichever occurs earlier. The investigator is required to report all treatment-related SAEs, regardless of whether or not the AE occurs after discontinuation of the study drug. The expected potential safety issues and the measures to be taken to avoid or minimize toxicity in this study will be summarized in the sections below.

5.1.1 Risks Associated with Toripalimab

Most adverse drug reactions by immune checkpoint inhibitors are due to effects of inflammatory cells on normal tissues. Generally, those risks refer to events mediated by potential inflammatory or immunity and may require more frequent monitoring and/or particular interventional measures, e.g., immune inhibitors and/or endocrine replacement therapy, The above immune-mediated effects may occur in almost all organ systems. Important identified risks of toripalimab therapy include but are not limited to immune-related interstitial lung disease, immune-related hepatic dysfunction, immune-related hyperthyroidism and hypothyroidism, immune-related hyperglycemia and diabetes, immune-related adrenocortical insufficiency, immune-related pituitary insufficiency, immune-related pancreatitis, immune-related myocarditis, infusion reactions, and allergic reactions. Important potential risks of toripalimab therapy include but are not limited to immune-related ocular toxicity and neurotoxicity, and reproductive embryotoxicity, etc. Under the established procedures for management of toxicity, the majority of immune-mediated AEs can be controlled.

See the current version of the Investigator's Brochure for a detailed summary of relevant safety data for toripalimab, including AEs, SAEs, and CTCAE Grade ≥3 events related with the investigational therapy, reported in the studies.

5.1.2 Risks Associated with Paclitaxel

The most common side effects of paclitaxel include bone marrow suppression, allergic reactions, neurotoxicity, cardiovascular toxicity, gastrointestinal reaction, and alopecia.

For more details on the safety profile of paclitaxel, please refer to the package insert.

5.1.3 Risks Associated with Cisplatin

Cisplatin is known to cause bone marrow suppression, ototoxicity and nephrotoxicity. Cisplatin-based chemotherapy is considered to cause moderately severe vomiting. Patients will be monitored for cisplatin-related AEs.

For more details on the safety profile of cisplatin, please refer to the package insert.

5.1.4 Overall Plan for Safety Management

5.1.4.1 Monitoring

In this study, the safety will be evaluated through monitoring of all the serious and non-SAEs. All AEs will be graded in accordance with National Cancer Institute [NCI] CTCAE 5.0. Safety assessments (including laboratory test results) will be carried out according to the study flow sheet in Appendix 1 Schedule of Assessments. Laboratory results must be reviewed before each infusion.

The general safety evaluation includes relevant medical history, physical examinations, and specific laboratory investigations, including serum biochemistry and complete blood counts (see Appendix 1 Schedule of Assessments and 2 for the schedule of study evaluations).

During the study treatment period, patients will be closely monitored for any symptoms and signs of autoimmune disease and infection.

All SAEs will be reported promptly (see Section 5.2.2). In addition, the independent data monitoring committee (IDMC) and medical monitors will review and evaluate any AEs observed on a regular basis.

The safety follow-up visit will be performed approximately 60 days after the last dose of study drug.

After the completion or early termination of treatment, patients with unresolved study treatment-related AEs will be followed until one of the following occurs: the AE resolves to

baseline; the AE is assessed as stable by the investigators; the patient starts a new anticancer therapy; the patient is lost to follow-up; the patient withdraws consent to remain on study; or the study drug or participation in the study is not considered to be the cause of the AE.

5.1.5 Dose Adjustment and Management of Adverse Events Related to Toripalimab/Placebo and Chemotherapeutic Drugs

5.1.5.1 Dose Adjustment of Study Drug

The dose of study drug will not be adjusted in this study. If an AE requiring dose interruption occurs, the study drug dosing can be interrupted for a maximum of 56 days from the last dose. If the AE leads to dose interruption of toripalimab for 56 days from the last dose, the study drug will be terminated and the patient will be followed up for safety and efficacy in accordance with Section 4.6.13.4.

If the patient is on treatment with glucocorticoids for treatment of AEs, the dose of study drug can be interrupted for more than 56 days to allow sufficient time for dose tapering of glucocorticoids until glucocorticoids are discontinued or the dose has tapered prednisone≤10 mg/day (or equivalent). The acceptable duration of dose interruption for patients requiring therapeutic glucocorticoids for more than 56 days must be agreed upon by investigators and medical monitors.

If the study drug is interrupted due to AE but the patient is otherwise stable without major organ dysfunction, chemotherapy can be continued after consultation with the Sponsor or their medical monitor. If the investigator judges that chemotherapy must be delayed due to chemotherapy-related AEs, administration of toripalimab may also be delayed.

5.1.5.2 Management of Adverse Events Related to Toripalimab

Toxicity that are related or possibly related to toripalimab should be managed in accordance with standard medical practices. Appropriate tests (e.g., autoimmune serological test or tissue biopsy) should be performed to determine possible immune-related causes of the AE.

Although most immune-mediated AEs observed after use of immunomodulators are mild and self-limited, they should be identified as early as possible and treated promptly to avoid potential serious complications. Resolution of the AE may not occur after temporary suspension or discontinuation of study drug in serious cases, a topical corticosteroid, systemic

corticosteroid, mycophenolate, or TNF-α inhibitor may be needed for immediate treatment of immune-mediated toxicity.

Refer to the section for information on management of irAEs and other special AEs in the Investigator's Brochure.

5.1.5.3 Dose Adjustment of Chemotherapy Drugs

At the start of each cycle, the absolute neutrophil count (ANC) should be ≥ 1.5×10^9/L and platelet count should be ≥ 100×10^9/L. The cisplatin or paclitaxel dose will be adjusted at start of subsequent cycles, based on the minimum platelet count and neutrophil count in the previous cycle. For treatment/retreatment criteria and dose adjustment criteria for paclitaxel and cisplatin, refer to Table 7 through Table 17 or adjust dose in accordance with local treatment practices at the discretion of the investigator.

Dose adjustment for chemotherapy is permanent; i.e., once the dose of paclitaxel or cisplatin is reduced, the reduced dose will be maintained or will be further reduced in subsequent cycles. A maximum of two dose reductions are allowed.

5.1.5.3.1 Dose Adjustment of Cisplatin

If patients have Grade 3 or 4 hematologic or non-hematologic toxicity (except for alopecia) after 2 dose reductions or if Grade 3 or 4 neurotoxicity is observed, cisplatin should be terminated.

- **Hematologic Toxicity**

The dose of Cisplatin can be delayed for a maximum of 3 weeks, if it is caused by hematological toxicity until ANC ≥ $1.5\times10^{\wedge9}$/L and platelet count >100×10^9/L on Day 1. If the ANC and platelet count are not recovered within 3 weeks, the dose of cisplatin should be reduced or interrupted according to the standard practice of the study site and at investigator's discretion, until appropriate recovery of ANC, otherwise the treatment will be terminated. See Table 7 for dose adjustment of cisplatin due to hematological toxicity.

Table 7 Dose Adjustment of Cisplatin for Hematologic Toxicity

Toxicity[a]	**Dose of Cisplatin**
ANC < 0.5×10^9/L and platelets ≥ 50×10^9/L	75% of previous dose
Platelets < 50×10^9/L, irrespective of ANC	75% of previous dose
Platelets < 50×10^9/L with ≥ Grade 2 hemorrhage, irrespective of ANC	50% of previous dose

ANC < 1.0×10^9/L, with fever ≥ 38.5ºC	75% of previous dose

ANC = absolute neutrophil count.

[a] nadir in previous cycles.

- **Non-hematologic Toxicity**

In case of ≥ Grade 3 non-hematological toxicity (except alopecia or neurotoxicity [not requiring termination of treatment]), cisplatin dosing should be interrupted until it is recovered to lower than or equal to pre-treatment level. The dose adjustment of cisplatin for non-hematological toxicity (except neurotoxicity, ototoxicity and nephrotoxicity) is detailed in Table 8.

Table 8 Dose Adjustment of Cisplatin for Non-hematologic Toxicity

Toxicity (except neurotoxicity, ototoxicity and nephrotoxicity)	Dose of Cisplatin
Any Grade 3 or 4 toxicity except alopecia	75% of previous dose
Diarrhea that requires hospitalization (regardless of grade) or Grade 3 or 4 diarrhea that requires appropriate antidiarrheals	75% of previous dose

- **Renal Toxicity**

It has been reported that renal impairment can occur when cisplatin is given alone or combined with other cytotoxic drugs. It is recommended that the CrCL must be ≥60 mL/min prior to the start of any cisplatin cycle. If CrCL is less than 60 mL/min at any time after day 1 in a treatment cycle and CrCL is ≥ 60 mL/min on Day 1 of the next cycle, the investigator should determine whether to continue cisplatin without dose adjustment, at a reduced dose, or to delay treatment based on clinical judgment. If CrCL has not recovered to ≥ 60 mL/min within 42 days after the last dose of the study drug, the investigator should consider permanent discontinuation of cisplatin.

- **Ototoxicity**

Ototoxicity has been observed when cisplatin is given alone or combined with other cytotoxic drugs. In case of ototoxicity, cisplatin doses should be interrupted until the results of audiometry shows auditory acuity is within a normal range[38].

- **Neurologic Toxicity**

Dose adjustment of cisplatin is recommended when neurotoxicity occurs. See Table 9 for the details.

Table 9 Dose Adjustment of Cisplatin for Neurologic Toxicity

Toxicity	Dose of Cisplatin
Grade 0 or 1 neurotoxicity	No dose adjustment
Grade 2 neurotoxicity	Reduce dose by 50% of previous dose
Grade 3 or 4 neurotoxicity	Permanent discontinuation

5.1.5.3.2 Dose Adjustment for Paclitaxel

The general principles for dose adjustment of paclitaxel during the study are as follows:

- If Grade 3 or 4 non-hematological toxicity occurs, the dose of paclitaxel can be reduced from 175 mg/m^2 to 140 mg/m^2 and further reduced to 110 mg/m^2 if necessary;
- If paclitaxel-related hypersensitivity occurs despite preventive medication, it should be treated according to medical indication;
- For CTCAE ≤ Grade 3 hypersensitivity, investigators will decide whether or not to continue paclitaxel treatment;
- For Grade 4 hypersensitivity, paclitaxel must be discontinued permanently;
- Paclitaxel-related fluid retention will be treated according to investigator judgment;
- If paclitaxel must be terminated prior to completion of the scheduled cycle, patients will continue to receive the study drug and cisplatin.

Dose adjustment of paclitaxel are displayed in Table 10.

Table 10 Dose Adjustment Levels for Paclitaxel

Chemotherapeutic drugs	Dose level 0 (starting dose)	Reduction by 1 dose level	Reduction by 2 dose levels
Paclitaxel (mg/m^2)	175	140	110

Dose adjustment for sensory neuropathy is shown in Table 11. Dose adjustment of paclitaxel for musculoskeletal pain that cannot be controlled with analgesics is shown in Table 12. Dose adjustment of paclitaxel for hematologic toxicity is shown in Table 13. Dose adjustment of

paclitaxel for hematologic toxicity is shown in Table 14. Dose adjustment of paclitaxel for non-hepatic gastrointestinal toxicity attributed to chemotherapy is shown in Table 15. Dose adjustment of paclitaxel for hepatotoxicity is shown in Table 16. Dose adjustment of paclitaxel for other clinically significant AEs is shown in Table 17.

Table 11 Dose Adjustment of Paclitaxel for Sensory Neuropathy[a]

Paresthesias/dysesthesias	**Lasting for 1-7 days**	**Lasting for >7 days or leading to delay of next cycle**
Grade 1: paresthesia/ hypoesthesia that does not interfere with function	No dose adjustment	Maintaining the dose of paclitaxel
Grade 2: paresthesia/ hypoesthesia that interferes with function but does not affect activities of daily living	No dose adjustment[b]	• InterruptionIf improved to ≤ Grade 1, reduce paclitaxel dose (dose of Paclitaxel reduced by 1 level, see Table 10 for the details); • For persistent Grade 2 requiring a dose delay of > 3 weeks, paclitaxel will be terminated;
Grade 3: paresthesia/ hypoesthesia with pain or functional impairment that interferes with the activities of daily living [d]	• First occurrence: reduce the dose of paclitaxel by 1 dose level • Second occurrence: permanently discontinue paclitaxel	Discontinuation of paclitaxel

[a] Dose adjustment of cisplatin for neurotoxicity is seen in Table 9;

[b] It must be resolved to ≤ Grade 1 on Day 1 of the next cycle of therapy;

[d] Paclitaxel should be terminated for persistent paresthesia/hypoesthesia that causes disability or endangers life.

Table 12 Dose Adjustment of Paclitaxel for Musculoskeletal Pain That Cannot Be Controlled With Analgesics[a]

Musculoskeletal pain	**Lasting for 1-7 days**	**Lasting for >7 days or leading to delay of next cycle**
Grade 1	No dose adjustment	No dose adjustment
Grade 2	No dose adjustment	No dose adjustment or delay next dose [b]
Grade 3	First occurrence: reduce the dose of paclitaxel by 1 dose level Second occurrence: permanently discontinue paclitaxel	First occurrence: delay next dose[b] or permanently discontinue paclitaxel Second occurrence: permanently discontinue paclitaxel

[a] It is encouraged to use morphine and non-steroidal anti-inflammatory drugs to maintain the dose of Paclitaxel when possible; adjustment of the dose level of Paclitaxel is seen in Table 10 in detail;

[b] Dose of Paclitaxel will be interrupted when persistent Grade 2 or 3 musculoskeletal pain occurs. If it is relieved to ≤ Grade 1, the dose of paclitaxel must be reduced when Paclitaxel treatment is resumed (reduction of dose of Paclitaxel by 1 level, see Table 10 for the details). If the Grade 2 or 3 toxicity still continues after the dose of Paclitaxel is delayed for 3 weeks, Paclitaxe l will be terminated;

Table 13 Dose Adjustment of Paclitaxel for Hematologic Toxicity[a]

CTCAE 5.0 grade	AE that occurs during treatment cycle and resolves prior to dose next cycle of therapy[b]	AE that occurs during treatment cycle and is present on the day of administration in next cycle of therapy
Neutropenia		
Grade 2, 3, or 4	No dose adjustment	Delay next dose[c] until ANC ≥1.5×10^9/L. Appendix 1 If recovery occurs in ≥1-3 weeks and G-CSF is not given: maintain previous dose and add G-CSF; Appendix 2 If recovery occurs within 1 week with G-CSF support, no dose adjustment is needed Appendix 3 If recovered occurs in 2-3 weeks with G-CSF support, reduce by 1 dose level.
Thrombocytopenia		
Grade 2 or 3	No dose adjustment	Delay next dose[c] until platelet count ≥100 × 10^9/L [1] If 1 week is needed for recovery: maintain the dose; [2] If 2-3 weeks is needed for recovery: reduce 1 dose level.
Grade 4	Reduce by 1 dose level	Reduce by 1 dose level

AE = adverse event; AGC = granulocyte; ANC = absolute neutrophil count; CTCAE = common terminology criteria for adverse event; G-CSF = granulocyte colony-stimulating factor

[a] The dose must be adjusted based on the AE that occurred during the previous treatment cycles (Column 2) and the AE that is still present on Day 1 of subsequent cycles (Column 3). The dose must be adjusted based on the AE requiring maximum dose adjustment; adjustment of the dose level of Paclitaxel is seen in Table 10 in detail;

[b] Resolution is defined as all AEs requiring dose adjustment on Day 1 of subsequent cycles of therapy (i.e., continue treatment without delayed dose) are ≤ Grade 1 [except ANC/AGC (must be ≥1500/mm^3) and bilirubin (must be ≤ baseline)];

[c] Interrupt dose of Paclitaxel and perform the test once per week. Except for ANC/AGC and bilirubin, the treatment will be resumed when the toxicity is ≤ Grade 1. If the toxicity is still not resolved when the dose is delayed for 3 weeks, Paclitaxel will be discontinued with cisplatin and study drug continued.

Table 14 Dose Adjustment of Paclitaxel for Neutropenic Fever[a]

CTCAE 5.0 grade	AE that occurs during treatment cycle and resolves prior to next cycle of therapy[b]	AE that occurs during treatment cycle and is present on the day of administration in next cycle of therapy
Neutropenia and fever		
Grade 3 or 4	Reduce by 1 dose level (see Table 10) and add G-CSF support or permanently discontinue paclitaxel.	

AE = adverse event; AGC = granulocyte; ANC = absolute neutrophil count; CTCAE = common terminology criteria for adverse event; G-CSF = granulocyte colony-stimulating factor.

[a] The dose must be adjusted based on the AE that occurred during the previous treatment cycle (Column 2) and the AE that is still present on Day 1 of subsequent cycles (Column 3). Dose adjustment must be based on the AE requiring the greatest adjustment. Whether the AE is "clinically significant" is to be determined by the investigator; adjustment of the dose level of Paclitaxel is seen in Table 10 in detail;

[b] Resolution is defined as all AEs requiring dose adjustment on Day 1 of subsequent cycles of therapy (i.e., continue treatment without delayed dose) are ≤ Grade 1 [except ANC/AGC (must be ≥1500/mm^3) and bilirubin (must be ≤ baseline)].

Table 15 Dose Adjustment of Paclitaxel for Gastrointestinal Toxicity Related to Chemotherapy Other than Hepatotoxicity[a]

CTCAE 5.0 grade	AE that occurs during treatment cycle and resolves prior to next cycle of therapy[b]	AE that occurs during treatment cycle and is present on the day of administration in next cycle of therapy
Diarrhea		
Grade 2	No dose adjustment	Reduce by 1 dose level
Grade 3	Reduce by 1 dose level	Reduce by 1 dose level
Grade 4	Reduce by 2 dose levels or discontinue paclitaxel	Reduce by 2 dose levels or discontinue palictaxel
Oral mucositis oral (stomatitis)		
Grade 2	No dose adjustment	Reduce by 1 dose level
Grade 3	Reduce by 1 dose level	Reduce by 1 dose level
Grade 4	Reduce by 2 dose levels or discontinue paclitaxel	Reduce by 2 dose levels or discontinue paclitaxel
Vomiting (regardless of receiving antiemetics)		
Grade 2	Reduce by 1 dose level (optional)	Reduce by 1 dose level
Grade 3 or Grade 4	Reduce by 1 dose level or discontinue paclitaxel	Reduce by 2 dose levels or discontinue paclitaxel

AE = Adverse event; AGC = granulocyte; ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events.

[a] The dose must be adjusted based on the AE that occurred during the previous treatment cycle (Column 2) and the AE that is still present on Day 1 of subsequent cycles (Column 3). The dose must be adjusted based on the AE requiring maximum dose adjustment (adjustment of the dose level of Paclitaxel is seen in Table 10 in detail). "Clinical significance" of an AE is to be determined by the investigator.

[b] Resolution is defined as all AEs requiring dose adjustment on Day 1 of subsequent cycles of therapy (i.e., continue treatment without delayed dose) are ≤ Grade 1 [except ANC/AGC (must be ≥1500/mm^3) and bilirubin (must be ≤ baseline)].

Table 16 Dose Adjustment of Paclitaxel for Hepatotoxicity[a]

CTCAE 5.0 grade	AE that occurs during treatment cycle and resolves prior to next cycle of therapy[b]	AE that occurs during treatment cycle and is present on the day of administration in next cycle of therapy
Elevated bilirubin or AST or ALP		
Grade 2	Reduce by 1 dose level	Delay dose[c] until bilirubin is recovered to baseline grade, AST and ALP are recovered to ≤ Grade 1 Resume at reduced dose by 1 dose level
Grade 3	Reduce by 2 dose levels	Reduce by 2 dose levels
Grade 4	Discontinue paclitaxel	Discontinue paclitaxel

AE = adverse event; AGC = granulocyte; ALP = alkaline phosphatase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CTCAE = common terminology criteria for adverse event.

[a] The dose must be adjusted based on the AE that occurred during the previous treatment cycle (Column 2) and the AE that is still present on Day 1 of subsequent cycles (Column 3). The dose must be adjusted based on the AE requiring maximum dose adjustment (adjustment of the dose level of Paclitaxel is seen in Table 10 in detail). "Clinical significance" of an AE is to be determined by the investigator.

[b] Resolution is defined as all AEs requiring dose adjustment on Day 1 of subsequent cycles of therapy (i.e., continue treatment without delayed dose) that are ≤ Grade 1 [except ANC/AGC (must be ≥1500/mm^3) and bilirubin (must be ≤ baseline)].

[c] Interrupt the dose, and perform the test once per week. Except for ANC/AGC and bilirubin, the treatment will be resumed when the toxicity is ≤ Grade 1. If the toxicity is still not resolved when the dose is delayed for 3 weeks, Paclitaxel will be discontinued and the other planned therapies can be completed continuously.

Table 17 Dose Adjustment of Paclitaxel for Other Clinically Significant AEs [a]

CTCAE 5.0 grade	AE that occurs during treatment cycle and resolves prior to next cycle of therapy[b]	AE that occurs during treatment cycle and is present on the day of administration in next cycle of therapy
Grade 3	Reduce by 1 dose level	Reduce by 1 dose level
Grade 4	Reduce by 2 dose levels or discontinue paclitaxel	Discontinue paclitaxel

AE = Adverse event; AGC = granulocyte; ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events.

[a] The dose must be adjusted based on the AE that occurred during the previous treatment cycle (Column 2) and the AE that is still present on Day 1 of subsequent cycles (Column 3). The dose must be adjusted based on the AE requiring maximum dose adjustment (adjustment of the dose level of Paclitaxel is seen in Table 10 in detail). "Clinical significance" of an AE is to be determined by the investigator.

[b] Resolution is defined as all AEs requiring dose adjustment on Day 1 of subsequent cycles of therapy (i.e., continue treatment without delayed dose) that are ≤ Grade 1 [except ANC/AGC (must be ≥1500/mm^3) and bilirubin (must be ≤ baseline)].

5.2 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording of AEs including SAEs, protocol-specified safety laboratory evaluation, measurement of protocol-specified vital

signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the investigational drug.

Some types of events need to be reported to the Sponsor immediately, as described in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for GCP, an AE is any untoward medical occurrence in a clinical investigation patient administering a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unexpected sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered to be related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9.
- The condition occurs intermittently and repeatedly (e.g., headache) and does not exist at baseline.
- Worsening of laboratory test results (e.g., ECG, X-ray) or other clinical findings leading to a change in administration of the study drug, including discontinuation of the study drug, or the need for concomitant medications to treat the AE.
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of the investigational drug (e.g., invasive procedures at screening such as biopsies)

5.2.2 Serious Adverse Events

An SAE is an AE meeting any of the following criteria:

- Leading to death (i.e., death is definitely caused by or resulted from the AE);
- Life threatening (i.e., the AE, in the view of the investigator, may jeopardize the patient at an immediate risk of death);
- Requiring inpatient hospitalization or prolongation of existing hospitalization (see Section 5.3.5.11);

- Leading to permanent or major disability/incapability (i.e., the AE causing substantial damage to patient's normal activities);
- Congenital deformity/birth defect in the newborn/infant of the mother using the investigational drug;
- Considered a significant medical event by the investigator (e.g., may jeopardize the patient's life or require medical/surgical intervention to prevent one of the outcomes listed above)

If an adverse event would be considered an SAE only after it worsens or results in death, the AE event would not be considered an SAE.

The terms "serious adverse event" and "severity of adverse event" are not synonyms. Severity is defined as intensity of an AE (judged in accordance with CTCAE 5.0); the medical significance of the event itself may be relatively small (e.g., severe headache without any other findings).

For each AE recorded on the eCRF, its severity and seriousness must be evaluated separately.

Investigators should report SAEs to the Sponsor immediately (i.e., within 24 hours after awareness of the event; see Section 5.4.1 for the report description).

5.2.3 Adverse Events of Special Interest (to be Report to the Sponsor Immediately)

The investigator will be required to report adverse events of special interest (AESIs) to the Sponsor immediately (i.e., within 24 hours after awareness of the event) (non-serious AESIs need not be reported to the regulatory authorities). AESIs of toripalimab include:

- Suspected immune-related myocarditis: elevated myocardial enzymes, change in ECG findings, or clinical symptoms;

- Events meeting the criteria for Hy's law, including ALT or AST >3× of baseline during treatment, with total bilirubin >2× ULN (where the direct bilirubin ≥35%); or ALT or AST > 3 × of baseline during treatment, with clinical jaundice; provided that cholestasis or hyperbilirubinemia caused by other reasons (see Section 5.3.5.7). have been excluded as alternative causes.

5.3 Methods and Timing for Capturing and Evaluating Safety Parameters

Investigators are responsible for ensuring that all the AEs (see Section 5.2.1 for the definition) are recorded in the Adverse Event page of the eCRF and reported to the Sponsor in accordance with the description in this section and Sections 5.4 to 5.6.

For each AE recorded in the eCRF of AE, investigators will evaluate its seriousness (see Section 5.2.2. for criteria for seriousness), severity (see Section 5.3.3) and causal relationship (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators should contact the patient to obtain information related to the AEs. All AEs, regardless of where it is reported by patients or identified by research staff, should be recorded in the patient's medical record and Adverse Event page of the eCRF.

Following signing of the ICF and prior to the first dose of the study treatment, only SAEs are to be reported.

After the start of study treatment, all the AEs will be reported (regardless of the relationship to the study drug) for up to 60 days after the last dose of the study treatment, initiation of a new antitumor therapy, patient withdrawal of consent, loss to follow-up, or death, whichever occurs first.

Sixty (60) days after the last dose or after the start of a new antitumor therapy (whichever occurs first, the investigator should report SAEs to the Sponsor when the investigator considers the SAE to be related to the study drug (refer to Section 5.6).

5.3.2 Collection of Adverse Events

A consistent methodology of non-directive questioning AE information should be adopted at all patient evaluation time points. Examples of non-directive questions are:

"How have you felt since your last clinic visit?"

"Is there any new health issue or change of health issue after your last visit?"

5.3.3 Severity Assessment of Adverse Events

The severity of AE will be evaluated with reference to CTCAE 5.0. If the occurrence of AEs does not fall within the scope of the criteria, Table 18 will be used to assess the severity.

Table 18 Severity Rating Scale for Adverse Events Not Listed in CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or no treatment required
2	Moderate; requiring minimal, local or non-invasive intervention; or limited age appropriate instrumental ADL[a]
3	Severe or medically significant, but not life-threatening immediately; requiring hospitalization or prolonged hospital stay; disability; or limited self-care ADL [b, c]
4	Life-threatening outcomes; requiring emergent treatment[d]
5	Deaths caused by an AE[d]

ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event.

Note: Based on the latest version of CTCAE 5.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

[a] Instrumental ADL refers to cooking, buying groceries or clothes, making telephone calls, and paying bills.

[b] Examples of self-care ADL include bathing, dressing, eating, going to the toilet, and taking medicines, which are activities that ambulatory patients can engage in.

[c] If an event is assessed as a "significant medical event", it must be reported as an SAE as described in Section 5.4.1.

5.3.4 Causality Analysis of Adverse Events

Investigators should comprehensively assess the causal relationship (related/unrelated) between an AE and the study treatment based on their understanding of the patient's medical history and clinical course of AE and after ruling out alternative causes. Related is defined as a reasonable relationship exists between the AE and study treatment; unrelated is defined as no reasonable relationship exists between AE and the study treatment but there are other explanations, for example, complications of underlying disease, PD, and concomitant therapy. The causal relationship between the AE and each treatment, i.e., toripalimab/placebo, paclitaxel and cisplatin, will be evaluated separately for the patients in the induction phase.

To determine the causal relationship, the following factors should be comprehensively considered:

- Temporal relationship between the occurrence of the event and the administration of study treatment
- The course of events, in particular, the impact of dose modification, discontinuation and rechallenge (if applicable) of the study drug,
- Known correlation between the event and the drug or products of the same class
- 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-therapeutic related factors known to be associated with occurrence of the event
- The investigator's assessment of causal relationship is one of the criteria for expedited reporting of suspected unexpected serious adverse reaction (SUSAR) by the Sponsor. The investigator should provide their medical judgment, in accordance with the information in the Investigator's Brochure for the investigational drug and based on comprehensive review of the available clinical evidence.

5.3.5 Recording Procedure of Adverse Events

Investigators should use correct medical terms/concepts to record AEs on the AE page of the eCRF. Avoid using verbatim or colloquial language and abbreviations.

In the event column on the AE page of the eCRF, only 1 AE term can be recorded for 1 event.

5.3.5.1 Infusion-related Reaction

Any AEs diagnosed as infusion-related reactions that occur during or within 24 hours of iv infusion should be recorded as a diagnostic result in the AE page of the eCRF (e.g., infusion-related reactions). Try to avoid using ambiguous terms such as "systemic reactions". If the patient experiences concurrent local and systemic reactions after administration of the study drug, each of the adverse reactions should be recorded, separately, in the AE page of the eCRF. In case of a local reaction, the term "injection site pain" or "injection site redness and swelling" should be used to clarify it.

5.3.5.2 Recording of AE Diagnosis, Signs and Symptoms

In addition to individual signs and symptoms, the diagnostic results (if known) should also be recorded in the AE page of the eCRF, such as only liver failure or hepatitis, but not jaundice, flapping fremitus, and elevated transaminases. However, if a single set of signs and/or symptoms cannot be medically diagnosed or diagnosed as a syndrome at the time of reporting, each event should be recorded in the AE page of the eCRF. If the diagnosis is subsequently confirmed, all previous events based on the diagnosis of symptoms and signs should be withdrawn and replaced with an AE report based on a single diagnosis, and the start date of the event is the start date of the initial symptom of the final diagnosis.

5.3.5.3 Adverse Events Occurring Secondary to Other Events

In general, for AEs that are secondary to other events (such as cascade events or clinical sequelae), their primary causes should be determined, with the exception of severe secondary AEs. If secondary AEs are medically significant with independent occurrence dates, the secondary event should be recorded as a separate event in the AE page of the eCRF. The following are examples:

- Vomiting should be reported in eCRF if the vomiting results in mild dehydration and no other treatment is required.
- If vomiting causes severe dehydration, these secondary events (dehydration) should be reported separately in the eCRF.
- If severe gastrointestinal bleeding causes renal failure, these secondary events should be reported separately in the eCRF.
- If dizziness leads to a fall and a subsequent fracture, these secondary and tertiary events should be reported in the eCRF.
- If neutropenia causes infection, these secondary events should be reported separately in the eCRF.

If it is not clear whether there is causality between the events, all AEs should be recorded separately in the AE page of the eCRF.

5.3.5.4 Persistent or Recurrent Adverse Events

Persistent AEs refer to the continuance of AEs that are not relieved between the assessment time points for each patient. Such events need only be recorded once in the AE page of the eCRF. When the event is first reported, the initial severity or grade of the event is recorded. If persistent AEs worsen, the maximum severity should be recorded in the AE page of the eCRF. If the AE meets the criteria for an SAE, the investigator must immediately report it to the Sponsor (i.e., within 24 hours after the awareness of aggravated event) (see Section 5.2.2 for reporting description) and update the AE page of the eCRF by changing the severity of the event from “non-serious” to “serious”, providing the date when the event was severe and filling in all the data related to the SAE.

Recurrent AEs are defined as the AEs that resolve at the time of the assessment compared with the last assessment (completely relieved), but subsequently recurred. Each recurrence of AEs should be recorded separately in the AE page of the eCRF.

5.3.5.5 Abnormal Laboratory Test Values

Not every laboratory abnormality is an AE. When an abnormal laboratory result meets any of the following criteria, it must be reported as an AE:

- Is accompanied with clinical symptoms;
- Leads to changes in study treatment (such as change in dose, treatment interruption, or discontinuation of treatment);
- Requires medical intervention (such as potassium supplement for hypokalemia) or a change in concomitant medications;
- Is clinically significant based on the investigator's judgment.

Note: For oncology studies, certain abnormalities need not be reported as AEs.

The investigator is responsible for reviewing all laboratory results to correctly judge whether an isolated abnormal laboratory test result should be regarded as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5× ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded in the AE page of the eCRF.

If an abnormal laboratory result is not a sign of a disease or syndrome, the abnormal result itself should be recorded in the AE page of the eCRF with an accompanying description specifying whether the test result is above or below the normal range (e.g., "high potassium" instead of "abnormal potassium"). If an abnormal laboratory result can be expressed with a precise clinical term according to the standard definition, the clinical term should be recorded as an AE. For example, if serum potassium elevates to 7.0 mEq/L, it should be recorded as "hyperkalemia".

If the same clinically significant laboratory abnormality is observed between visits, only 1 AE should be counted in the AE page of the eCRF (see Section 5.3.5.4 for details on persistent AEs).

5.3.5.6 Abnormal Vital Signs

Not every abnormal vital sign is an AE. When the result of a vital sign meets any of the following criteria, it must be reported as an AE:

- Is accompanied with clinical symptoms;
- Leads to changes in investigational therapy (such as dose adjustment, treatment interruption, or termination of treatment);
- Requires medical intervention or changing concomitant medications;
- Is clinically significant based on the investigator's judgment.

The investigator is responsible for reviewing all vital sign findings to correctly judge whether an isolated abnormal vital sign should be regarded as an AE.

If a clinically significant abnormal vital sign indicates a certain disease or syndrome (e.g., hypertension), only the diagnostic result (i.e., hypertension) needs to be recorded in the AE page of the eCRF.

If the same clinically significant abnormal vital signs are observed at each visit, they should not be duplicated in the AE page of the eCRF unless the etiology changes (for details on recording persistent AEs, see Section 5.3.5.4).

5.3.5.7 Abnormal Hepatic Function Test Findings

Elevated ALT or AST (>3× ULN) accompanied by elevated total bilirubin (>2× ULN) or clinical jaundice which cannot be explained by cholestasis or other medical conditions should be considered as drug-induced liver injury (according to Hy's Law). Therefore, when any of the following occurs, the investigator must report it as an AE:

- ALT or AST >3× ULN during treatment with total bilirubin >2× ULN (direct bilirubin ≥35%);
- Treatment-emergent ALT or AST >3× ULN with clinical jaundice.

The diagnosis or laboratory abnormal results (if no clear diagnosis can be made) will be recorded as SAEs in the AE page of the eCRF and immediately reported to the Sponsor (i.e., within 24 hours of the awareness of the event).

5.3.5.8 Death

In this protocol, death is the endpoint for the efficacy objective of overall survival. A death that occurs within the AE reporting timeframe specified in the protocol (see Section 5.3.1, from start of screening until 60 days after the last dose of the investigational drug) and is caused only by progression of ESCC, as assessed by the investigator, should be recorded as "PD" in the eCRF for AEs. The severity of such AE is recorded as Grade 5 (refer to NCI CTCAE 5.0) and the outcome is recorded as fatal. Death should be reported immediately to the Sponsor. After the AE reporting period as specified in the protocol (refer to Section 5.3.1, after the period of 60 days after the last dose of the investigational drug), a death resulted from PD will not be reported as an AE and should be recorded in the Follow-up eCRF page instead.

All the other events leading to deaths, occurring during the study, irrespective of the relationship with the investigational drug, should be recorded in the eCRF for AEs, and reported to the Sponsor immediately. Death should be regarded as the outcome of event rather than the event itself. The event or disease leading to or facilitating the outcome of death should be recorded as 1 single medical concept in the eCRF of AE. Generally, only 1 such event should be reported.

The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event CRF. If the cause of death is known afterwards (e.g., following autopsy), the confirmed cause of death will be used to replace "death of unknown cause".

5.3.5.9 Pre-existing Disease Conditions

The pre-existing disease means that the disease state already exists at the screening visit of this study. The preexisting disease should be recorded in the eCRF as part of medical history and baseline condition. See Appendix 11 for a detailed listing of pre-existing autoimmune diseases, which may preclude eligibility for the study.

During the study period, only when the frequency, severity, or nature of the pre-existing medical condition has deteriorated should it be recorded as an AE. When such an event is

recorded in the AE page of the eCRF, care should be taken to adopt a suitable description to convey the concept that the pre-existing medical disease has changed (e.g., “more frequent headaches”).

5.3.5.10 Lack of Efficacy

Events that are clearly consistent with the expected progression pattern of disease under study should not be recorded as AEs. These data will only be collected as efficacy analysis data. In most cases, the expected progression pattern will be assessed based on radiological evaluation criteria (e.g., RECIST 1.1). In rare cases, it will be determined whether there is clinical progression based on the worsening of symptoms. However, objective criteria should be used to justify progression. If it is uncertain whether an event is attributed to an AE, the event should be reported as an AE.

5.3.5.11 Hospitalization or Prolongation of Hospitalization

Any AE leading to hospitalization (i.e., inpatient admission) or prolonged hospitalization should be documented and reported as an SAE (as defined in Section 5.2.2, Serious Adverse Events), with the following exceptions:

- Hospitalization due to temporary medical care;
- Hospitalization as scheduled in study protocol (e.g., for investigational drug administration or for evaluation of the efficacy of this study);
- Hospitalization due to preexisting conditions, but all the following criteria must be met:
    a) Hospitalization is already planned prior to the study, or hospitalization for elective surgery is needed due to expected normal disease progression during the study.
    b) The patient has not experienced any AE.
    c) Hospitalization only due to related cancer progression.

If a patient is hospitalized because they need medical treatment outside of normal outpatient business hours, then the hospitalization will not be considered to meet the criterion for an SAE.

5.3.5.12 Adverse Events in Association With Overdose/Medication Errors

Overdose refers to accidental or intentional administration at higher doses than those currently being studied. Overdose or improper dose of the investigational drug itself will not

be regarded as an AE, and the information on the medication should be recorded on the medication page of the eCRF. AEs associated with overdose or incorrect administration of the investigational drug will be considered as SAEs and will be recorded in the AE page of the eCRF and reported immediately to the Sponsor (i.e., within 24 hours after the awareness of the event). Please refer to Section 5.4.1.

5.3.5.13 Data on Patient-reported Outcomes

The data source of AE reporting does not include the PRO data received by the Sponsor, and PRO data will not be used for analysis of safety. However, when any PRO data that is possibly indicative of an AE is found in reviewing the PRO data at the research site, investigators need to determine whether it meets the criteria of an AE and record this event on the AE page of the eCRF if it meets.

5.4 Immediate Reporting Requirements (Within 24 Hours) From Investigators to the Sponsor

Regardless of the causality, investigators must report the following events to the Sponsor within 24 hours after being aware of them:

- SAE
- AESI
- Pregnancy

Investigators must report the important new follow-up data on these events to the Sponsor immediately (i.e., within 24 hours after awareness of the events). Important new information includes the following:

- New sign or symptom or change in diagnosis;
- Important new results of laboratory tests;
- Change of causality based on the new data;
- Change in the outcome of event, including recovery;
- Other narrative data on the clinical course of the event.

Investigators also have to follow relevant requirements on SAE reporting according to local health regulatory authorities and IRC/EC.

5.4.1 Serious Adverse Event Reporting Requirements

5.4.1.1 SAE Occurring Before the Start of the Study Treatment

All SAEs occurring after signing informed consent until 60 days after the last dose of study drug must be reported. Investigators should complete the SAE report form and submit it to the Sponsor or the designated person immediately (i.e., within 24 hours after awareness of the event) via fax or email.

5.4.1.2 SAE Occurring After the Start of Study Treatment

All serious adverse events occurring at any time after the first dose of study drug through 60 days after the last dose of study treatment, initiation of a new antitumor therapy, patient withdrawal of consent to remain on study, loss to follow-up, or death, whichever occurs first, must be reported. Investigators should complete the SAE report form and submit to the Sponsor or the designated person immediately (i.e., within 24 hours after awareness of the event) via fax or email.

See Section 5.6 for a description of the required AE reporting after the study.

5.4.2 Reporting Requirements for Pregnancies

5.4.2.1 Pregnancy of Female Patients

The female patients of childbearing potential shall be informed to notify investigators immediately if they are pregnant during the study or within 90 days after the last dose of the investigational drug. Investigators should fill in the pregnancy report form immediately (i.e., within 24 hours after awareness of pregnancy) and submit to the Sponsor. Investigators should discontinue dosing of the investigational drug and discuss with the patient about the risk of pregnancy and possible effect on the fetus. Monitoring should be continued until conclusion of the pregnancy. Pregnancy will not be recorded as an AE, however, a pregnancy-related SAE (e.g., fetal event, SAE in the mother during or resulting from the pregnancy, or congenital deformity/birth defect in children) should be reported in the AE page of the eCRF. In addition, following acquisition of the updated information on the course and outcome of pregnancy, investigators will submit the pregnancy report form under this trial.

5.4.2.2 Pregnancy of Female Partners of Male Patients

Male patients must also be instructed in the ICF to immediately inform the investigator if their female partner becomes pregnant during the study or within 90 days after the last dose of the study drug. Investigators should fill in the pregnancy report form immediately (i.e., within 24 hours after awareness of pregnancy) and submit to the Sponsor. The investigator should make every effort to collect and report detailed information on the course and outcome of the pregnancy. The pregnant partner will be asked to a letter authorization disclosure of pregnancy-related medical information and to allow follow-up for her pregnancy in order to update the pregnancy report form. Investigators contacted by male patient or his pregnant partner can provide the treating physician and/or obstetrician with information on the potential risk to the fetus, and make the informed decision jointly.

If the electronic data capture (EDC) system is not available, it will be reported in accordance with the report description provided in Section 5.4.2.1.

5.4.2.3 Abortion

Any abortion (except induced abortion) should be classified as an SAE (as the Sponsor considers abortion to be an adverse event of medical significance), recorded in the AE page of the eCRF, and reported to the Sponsor immediately (i.e., within 24 hours after awareness of the event) (see Section 5.4.2).

5.4.2.4 Congenital Anomaly/Birth Defect

If the congenital deformity/birth defect occurred in the fetus delivered by the female patient using the investigational drug or female partner of male patient using the investigational drug, it should be classified as an SAE, recorded in the AE page of the eCRF, and reported to the Sponsor immediately (i.e., within 24 hours after awareness of the event; see Section 5.4.2).

5.5 Follow-up for Patients Following Adverse Events

5.5.1 Investigator Follow-up

Investigators should follow up all AEs, until resolution or stabilization of the AE, patients' loss to follow-up, initiation of a new antitumor therapy, death, termination of the study by the Sponsor or patient's withdrawal of consent to remain on study, whichever occurs first. Every effort should be made to follow up all the SAEs related to the investigational drug or study procedures, until the final outcome can be reported.

During the study, resolution of AE (and the date of recovery) should be recorded on the AE page of the eCRF and patient's medical record, as to facilitate validation of source data. If the outcome of the AE is unclear from the information collected by follow-up, it should be stated on the AE page of the eCRF.

All pregnancies reported during the study should be followed up until the termination of pregnancy.

5.5.2 Sponsor Follow-up

For SAE, AESI, and pregnancy, the Sponsor or the designated person can acquire case-related information and its outcome via telephone, fax, email, and/or monitoring visit (e.g., from discharge note, consultation report, autopsy report) to facilitate independent medical evaluation of these reported cases.

5.6 Post-study Adverse Events

After a period of 60 days after the last dose or start of a new antitumor therapy, whichever occurs first, any SAE considered to be related with the previous treatment with investigational drug should be reported by the investigator until patients' withdrawal of the informed consent, lost to follow-up, or death.

If the EDC system is not available, investigators can use the provided fax number or email address to send the SAE/AESI report form directly to the Pharmacovigilance Department of Shanghai Junshi Biosciences Co. Ltd. or its designated email address.

5.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Board, and Ethics Committee

Based on the accumulated experiences of products, the Sponsor will evaluate all the SAEs and AESIs in real-time, identify SUSAR, and communicate immediately with the investigator, the institutional review board, and the health regulatory authorities in accordance with regulatory requirements.

In order to determine the requirement for reporting single AE case, the Sponsor will use the Investigator's Brochure on toripalimab as the reference to evaluate the predictability of these events.

The Sponsor will compare the severity and cumulative event frequency of each event reported in this study with what is recorded in the applicable reference document.

The reporting requirement will also be based on the evaluation of relationship and seriousness by investigators, and the Sponsor is allowed to update it when required.

The Sponsor shall strictly implement the expedited reporting in accordance with the requirements of "Good Clinical Practices (Administration Decree No.3) – Clause 40, the applicant and the investigator should investigate rapidly any serious adverse event occurred, and adopt essential measures to ensure safety and rights of patients, and to report to the drug supervision and administration authorities and health administration authorities immediately as well as to circulate to other investigators involved in the clinical trials of the same drug".

6 Statistical Considerations and Analytical Plan

6.1 Determination of Sample Size

Approximately 500 patients with advanced or metastatic ESCC who have not received systemic chemotherapy previously will be enrolled in this study and randomized in a ratio of 1:1 into the toripalimab combined with TP regimen (Group A) and placebo combined with TP regimen (Group B).

The sample size was calculated based on the dual —primary efficacy endpoints of PFS as evaluated by BICR per RECIST 1.1 and OS.

A hierarchical testing will be used for PFS and OS analysis at an overall significance level of two-sided 0.05, i.e., all the α levels (two-sided 0.05) will be firstly used for the hypothesis test of PFS, and when the null hypothesis of PFS is rejected, the hypothesis test of OS will be conducted at the 2-sided 0.05 significance level.

For PFS, 283 PFS events are expected to be observed in approximately 500 patients enrolled approximately 24 months after randomization of the first patient. This will provide 85% statistical power to detect an improvement in PFS for toripalimab in combination with TP vs placebo in combination with TP in patients with advanced or metastatic ESCC who have not previously received systemic chemotherapy at the two-sided significance level of 0.05 to detect a corresponding hazard ratio (HR) of 0.7.

[]For OS, 366 OS events are expected to be observed in approximately 500 patients enrolled approximately 39 months after randomization of the first patient, thereby there is 85%

statistical power to detect an improved OS for toripalimab in combination with TP vs placebo in combination with TP in patients with advanced or metastatic ESCC who have not previously received systemic chemotherapy at the two-sided significance level of 0.05 to detect a corresponding HR of 0.73. One planned interim analysis of OS will be performed at the time of the PFS analysis (approximately 24 months after randomization of the first patient).

Calculation of the above sample size is based on the following assumptions:

- PFS and OS appear exponential distribution;
- The median PFS in Group B is 5 months and the median OS is 10 months;
- α-consumption function of O'Brien-Fleming type (approximation using Lan-DeMets method) is used for interim analysis and primary analysis of OS, to control the overall type I error rate;
- Approximately 500 patients will be recruited within 22 months;
- For observation of PFS and OS events, the drop-out rate is 5% within 1 year after randomization.

6.2 Data Analysis Sets

ITT set: All the randomized patients.

Safety analysis set (SS): In the ITT set, all the patients who have received any dose of the investigational drugs (including toripalimab or chemotherapy).

6.3 Analytical Method

The standard descriptive statistical results include median, mean, standard deviation, minimum, and maximum for continuous variables, and number and percentage for categorical variables.

The detailed statistical plan and method shall be described in detail in a separate Statistical Analysis Plan.

6.3.1 Demographics and Baseline Disease Characteristics

Demographic and baseline disease characteristics data shall be summarized by the above descriptive analysis method.

6.3.2 Efficacy

All efficacy data shall be analyzed, based on the ITT analysis set.

6.3.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the dual endpoint comprised of PFS (as evaluated by BIRC in accordance with RECIST 1.1) and OS. In this study, hierarchical testing method will be used for the analysis of PFS and OS, i.e., all the α levels (2-sided 0.05) will be firstly used for the hypothesis test of PFS, when the null hypothesis of PFS is rejected, the hypothesis test of OS will be conducted at the two-sided significance level of 0.05. The null hypothesis and alternative hypothesis of PFS and OS analyses can be represented by the corresponding survival function $S_A(t)$ in Group A and the survival function $S_B(t)$ in Group B:

H_0: $S_A(t) = S_B(t)$ vs H_1: $S_A(t) \neq S_B(t)$.

PFS is defined as the time from randomization to first recorded PD or to death for any cause, whichever occurs earlier. Patients with no PD or death will be censored on the day of the last complete tumor assessment evaluation. Patients who have not undergone any post-treatment tumor evaluations during the study and with no death recorded will be censored 1 day after randomization. Patients who do not report any PD nor start any anticancer therapy unspecified in the protocol will be censored on the day of the last evaluable tumor evaluation prior to the start of subsequent anticancer therapy. PFS analysis will be conducted by the stratified log-rank test method, and the stratification factors include ECOG performance status score (0 or 1) and previous radiotherapy (yes or no). The Kaplan-Meier (KM) method will be used to estimate the median PFS in each treatment group; the 95% CI of median PFS will be estimated through the Brookmeyer-Crowley method using log-log function conversion to reach normal approximation. The HR of PFS and its 95% CI will be estimated using the stratified Cox proportional hazard model.

The OS is defined as the time from randomization to death for any cause. Patients without death recorded will be censored on the last known survival date. Patients without any follow-up information will be censored on the day after randomization. The same analytical method for PFS will be used for analysis of OS.

6.3.2.2 Secondary efficacy endpoints

The secondary efficacy endpoints include ORR, DCR, DOR, and TTR evaluated by BICR or by the investigator in accordance with RECIST 1.1; PFS evaluated by the investigator in accordance with RECIST 1.1; and PFS, ORR, DCR, DOR and TTR evaluated by the investigator in accordance with irRECIST, as well as the 1- and 2-year PFS and OS rates. The specific definition is as follows:

- The PFS rate at 1 year or 2 years is defined as the percentage of patients who are alive and have no documentation of PD within 1 year or 2 years after randomization.
- The OS rate at 1 year and 2 years is defined as the percentage of patients who are alive within 1 year or 2 years after randomization.
- The ORR is defined as the proportion of patients with a best overall response of CR or PR.
- DCR is defined as the proportion of patients with a best overall response of CR, PR, or SD.
- DOR is defined as the time from first documented objective response (CR or PR) to first recorded PD or to death, whichever is earlier. DOR is analyzed only for the patients with the best overall response of CR or PR. Patients without progression or death after achieving response will be censored on the date of the last tumor assessment. If no tumor assessment is performed after achieving response, the patients will be censored 1 day after the tumor assessment upon response.
- TTR is defined as the time from randomization to first documented objective response (CR or PR). TTR will be calculated only for the patients with the best overall response of CR or PR, without censoring.

The analytic methods used for the primary efficacy endpoints of PFS and OS will be used for analysis of the secondary efficacy endpoints of DOR and TTR. The percentage of patients in each treatment group will be calculated for ORR and DCR. The Clopper-Pearson method will be used to calculate their 95% CIs, and the 95% CI for the difference in the percentage between groups will be estimated using the NEWCOMBE method. The KM method will be used to estimate the PFS and OS rate at 1 year and 2 years in each treatment group. The 95%

CIs will be estimated using the Greenwood formula, and the 95% CI for the intergroup difference in PFS and OS rate will be estimated using the Newcombe method.

6.3.3 Safety

All safety data will be summarized based on the safety analysis set.

AEs will be summarized by the system organ class and preferred term (PT) of the Medical Dictionary for Regulatory Activities. The summaries for correlations of SAEs and AEs, severity of AEs, and irAEs will be tabulated.

Vital signs data, ECG data, laboratory test data, and physical examination data shall be tabulated by time.

A frequency form will be used to summarize the occurrence of AEs and the number and incidence of abnormal laboratory tests. Severity and relationship to the investigational drug will be tabulated for each AE and abnormal laboratory value. Descriptive statistics will be used to summarize the laboratory test results and vital sign indicators of each visit by group.

The safety of toripalimab will be evaluated by analyzing the occurrence of AEs in combination with the vital signs and laboratory test results during the drug administration.

6.3.4 Exploratory Analysis

- To explore the correlation between the biomarkers in archived or fresh tissue specimen and blood (including but not limited to PBMC, PD-L1, EBV, MSI, 11q13, tumor mutation burden, and other) and disease status, mechanism of resistance and/or response to toripalimab.
- To evaluate the incidence and titer of ADA of toripalimab and to explore the potential correlation between the immunogenicity response and PK, safety, and efficacy
- To evaluate the practicability of biopsy when obvious PD appears to differentiate the obvious increase of tumor volume related to the immunoregulatory activity of toripalimab (i.e., pseudo-progression/ tumor immune infiltration) and real PD.

6.4 Interim Analysis

One interim analysis of OS is planned to be conducted in this study.

The interim analysis of OS is to be conducted at the time of the PFS analysis, i.e., when approximately 283 PFS events and 212 OS events have occurred, respectively, which is expected approximately 24 months after the first patient is randomized. However, the exact timing of this analysis will depend on the actual time when the number of PFS events required for PFS analysis is reached.

The interim analysis will be performed by independent statistical analysis service provider, the result of the interim analysis will be reviewed by IDMC and advice will be provided to the Sponsor thereafter.

7 Data Collection and Management

7.1 Quality Assurance of Data

The Sponsor will entrust a contract research organization (CRO) to conduct data management of this study, including verification of the data quality. Patients' data will be collected through EDC system using eCRF. The research site is responsible for data entry to EDC system. If a discrepancy is found in the data, the Sponsor will request the research site to clarify, and any correction or clarification must be done in EDC system.

The Sponsor will establish the procedures on how to ensure the quality of data captured in the EDC. The central laboratory will transfer the data to the Sponsor directly, and the electronic transmission of these data will be conducted according to the Sponsor's SOP.

The audit trail control feature of EDC system will be used to keep a record of change and corrections made to eCRF. The data backup and study record retention will be conducted by the Sponsor according to the Sponsor's SOP.

7.2 Electronic Case Report Form

eCRF will be filled by the EDC system designated by the Sponsor. The research sites will be trained on how to fill out the eCRF. The eCRF will be submitted electronically to the Sponsor according to the procedures defined by the Sponsor.

All eCRFs must be completed by the designated and trained staff of the research site. The investigator or designee will review the eCRF, and the investigator will sign electronically.

At end of the study, the investigator will receive patients' data of the research sites through a read-only disc and will be stored with the study records. The return receipt for the disc must be signed.

7.3 Source Documents

The study monitor will carry out continuous verification of source data to ensure that the key data (i.e., source data) from source documents are entered in eCRF accurately and completely by authorized staff at the study site and ready to be verified.

Source documents (paper or electronic) refer to verified first-hand data of patients. Source documents include but are not limited to hospital records, clinical and outpatient medical records, laboratory records, memos, patients' log or PRO, list of assessments, pharmacy dispensation records, data recorded in the automatic instruments, copies that are verified to be true and exact to the original documents, microfiches, photographic plates, microfilms or magnetic media, X-ray photography, patients' documents, and records stored in pharmacies, laboratories, and medical technical departments participating in the clinical study.

Prior to start of the study, the types of source documents that are acceptable must be defined clearly in the Study Monitoring Plan, including protocol data directly entered into eCRF (i.e., written or electronic data previously not existing) and any other media considered as source data.

Alteration or destruction of the source documents required to verify validity and integrity of the data entered in eCRF is prohibited. Source documents must be stored in accordance with the record retention policies as described in Section 7.5.

The investigator and the research site must grant the Sponsor, EC and regulatory authority direct access to source documents for audit, review or inspection.

7.4 Use of Electronic Data Capture Systems

When the clinical results are directly entered into the electronic data capture (computer) system for medical records for the trial center (i.e., instead of the original hard copy records), the electronic records may be used as source documents, if the computer system has been validated in accordance with the regulatory requirements for computer system used in clinical studies. If the original data are changed, then the system should retain visible audit trails, which can show the original data and the reasons for changes, name of the modifier, and the date of change.

7.5 Records Retention

Trial-related records and files, including eCRF, PRO data, ICFs, laboratory test results, and study drug inventory records, must be retained by the principal investigator for at least 15 years after study completion or termination or for a period as required by the national or local regulatory authorities, whichever is longer. After the retention period, the above documents may be destroyed in accordance with local laws and regulations.

The records should not be disposed without written permission by the Sponsor. A written notice should be submitted to the Sponsor before any records are transferred to a different location.

8 Ethical Considerations

8.1 Compliance

This study shall be carried out in strict accordance with the laws and regulations for clinical studies in China, including GCP, Declaration of Helsinki (edition 2013), and other regulations, as well as this study protocol. The specific procedures for implementation of the study shall be in accordance with the SOPs of all organizations/collaborators in participating the study.

8.2 Informed Consent

The Sponsor’s template of ICF will be provided to each site. Prior to submission to EC, the Sponsor or its designated personnel must review and approve any modification to the Sponsor’s template of ICF or any alternated consent form provided by the research site (collectively referred to as “informed consent form”). As required locally, the final consent form approved finally by EC must be provided to the Sponsor for submission to health authorities.

The ICF includes a separate section involving collection of optional samples and use of remaining samples (plasma, serum, whole blood, and tissue), which are used for the optional exploratory study. The investigator or designee will explain to patients the relevant purposes, methods, and potential risks of each optional procedure. The patients are informed that they may voluntarily refuse to participate in the study, withdraw the informed consent at any time, and/or request to withdraw sample for any reason during the storage. It is required to provide a separate signature specifically to record that the patients agree for collection of optional

samples and use of any remaining samples for the exploratory study. Patients who refuse to participate do not need to provide a separate signature.

The informed consent shall also contain the following additional signature page:

- If approved by the investigator and the Sponsor's medical monitor or designated representative, patients in the toripalimab/placebo group who choose to continue the treatment after the first radiologically documented PD and who meet the criteria described in Section 4.7.2 shall sign on this page. Prior to consent, the patients will be informed by the investigator of other available treatment options and potential risks of continued treatment.

An optional ICF for collection of tumor tissue sample at the time of PD must be by the patient to provide consent for biopsy at the time of disease progression. For details, see Section 4.6.11.2.

The patient or his/her legal representative must sign the ICF and date prior to patient's participation in the study. The process of obtaining informed consent must be recorded in each patient's medical record or clinic record and must be completed before participation in the study.

If the study procedure is changed or new information that may possibly affect patient's willingness to participate in the study is acquired, the ICF should be revised. The revised ICF must be approved by IRB/EC before use and submitted to regulatory authorities.

During participation in the study, all revised versions of consent forms must be re-signed by the patients (or consent on important new information/results appendix in accordance with applicable laws and EC policies). The process of re-consenting must be documented.

A copy of the signed consent form must be provided to the patient or his/her legally authorized representative. All the signed and dated ICFs must be kept in the patient's study document or site document and can be provided to study monitors for verification at any time.

8.3 Ethic Committee

Prior to initiation of the study, the investigator must provide the study protocol, ICF, and any information to the patients to the EC for review and approval. In addition, all materials for recruitment of patients must be approved by the EC.

In accordance with the laws and regulations, policies, and relevant requirements by EC, the principal investigator shall submit a written progress report for the study at least annually to the EC. The investigator is also responsible in notifying EC for information of any amendment of the study protocol (see Section 9.6).

In addition to reporting all AEs to the Sponsor, the investigator must report SAEs to local regulatory authorities and EC in accordance with the requirements. The investigator may receive the written safety report for the study drug or other safety related correspondences from the Sponsor. The investigator is responsible for reviewing and processing of these reports in accordance with the requirements by regulatory authorities and policies and procedures established by EC. Safety reports will be archived at the research site.

8.4 Principles of Maintaining Confidentiality

To protect the patients' privacy, the Sponsor assigns a unique patient ID for each patient enrolled into the study. This means that the patient's name will not be included in the data set delivered to the Sponsor.

The patients' medical information obtained in the study are confidential and can be disclosed to a third party only as allowed in the ICF (or a separate letter of authorization for use of personal healthy information) signed by the patients.

For treatment purposes, the medical information may be provided to the patient's own doctor or other healthcare professionals who are attending the patient.

The representative of the national or local health regulatory authorities, the medical monitor, representative or collaborators of the Sponsor, or EC of each research site may request access to the data obtained from the study at any time.

8.5 Financial Disclosure

The investigator will provide adequate and accurate financial information to the Sponsor in accordance with the local laws and regulations so that the Sponsor may submit a complete and accurate financial proof or disclosure statement to the health regulatory authorities. The investigator shall provide the information on financial interests during the study and within 1 year after completion of the study.

9 Study Records, Monitoring and Management

9.1 Study Records

The investigator must keep adequate and accurate records so that the implementation process of the study has complete written records, including but not limited to the study protocol, protocol amendments, ICF, and approval documents by EC and government. In addition, the investigator will receive patient's data at the end of study, including audit trails for the records for all data changes.

9.2 Protocol Deviations

The investigator should record and explain any deviation from the protocol. In accordance with the established EC policies and procedures, the investigator should report any deviation that may influence patients' safety and data integrity to the Sponsor and EC.

9.3 Quality Control and Quality Assurance

In order to ensure quality of the trial, the clinical study plan is discussed and established jointly by the Sponsor and the investigators prior to the official initiation of the formal study. Relevant investigators participating in the study are trained according to GCP.

Each research site must manage the study drug according to the SOPs, including receipt, storage, dispensation, and retention.

9.3.1 Monitoring

The clinical monitor authorized by the Sponsor shall have the right to consult the eCRF, ICF, and all original source data.

The clinical monitor shall be responsible for formulating the plan and procedures that must be followed during the study. An on-site visit shall be carried out prior to initiation of the study. A regular visit shall be made during performance of the study. If needed, the patient may be contacted via telephone, fax, or mail, as supplement to the on-site visit.

Prior to initiation of the study, the investigator shall be notified of the expected frequency of monitoring visits. Additionally, during the study, the investigator shall be notified in advance prior to each monitoring visit. The visit is intended to ensure that the clinical study shall be carried out in strict accordance with the study protocol and to ensure the integrity and accuracy of the case report form, which may be verified from the original documents.

The clinical monitor shall check that all eCRFs are filled out correctly and completely and are consistent with the original data; all the errors and missing data have been modified or noted,

signed, and dated by investigators. At each visit, the investigator and the clinical monitor shall cooperate closely, to check and verify the case report form, drug supply and inventory records, drug distribution and recovery records, and other scheduled additional records.

The Sponsor or a person authorized by the Sponsor may check the quality of the study; the checker has the right to examine all study-related medical records, investigator's files and correspondences, and ICF.

9.3.2 Auditing

When appropriate, the auditor shall conduct an audit of the study according to relevant SOPs, to ensure that the study is carried out in accordance with the national relevant laws and regulations, SOPs, and the protocol. The audit range includes office documents and the research site's documents. After the audit, the auditor shall submit a written report to describe any problem found and propose suggestions; relevant persons (investigator and auditor) shall adopt corresponding corrective measures and record them in writing.

9.4 Administrative Management Structure

This study is sponsored and managed by Shanghai Junshi Biosciences Co., Ltd. Approximately 500 patients will be randomized.

Randomization is conducted by the IxRS. The site facilities will be used for evaluation (e.g., designated laboratory examinations) throughout the study. For routine study examinations, a locally certified laboratory will be responsible for implementation; the normal laboratory test ranges for the local laboratory will be collected.

9.5 Publication of the Data and Protection of Commercial Confidential Information/Trade Secrets

The investigator shall keep information and data related with the study confidential and shall not cite or publish study results or data without permission of the Sponsor.

The Sponsor has the right to issue or publish information or data related to the study or submit them to NMPA. The Sponsor shall seek permission of the investigator if the investigator's name will appear in the publication or other content.

9.6 Protocol Amendment(s)

Protocol amendments will be submitted to the EC in accordance with the provisions of the local laws and regulations.

Prior to implementation of any change in the protocol, the revised protocol must be approved by the EC (according to local requirements), unless the change is to eliminate any direct hazard to patients or is only a change in logistics or personnel (e.g., change of medical monitor or contact information).

10 Independent Data monitoring Committees (IDMC)

An IDMC will be set up to assess safety data and conduct efficacy assessment and benefit-risk assessment of this study. The IDMC will include at least 2 clinicians and 1 biostatistician with professional knowledge on oncological trials. Prior to the final analysis of PFS, risk/benefit assessments will be conducted at regular data review meetings to ensure the safety of the patients. The IDMC will also review the efficacy data from any planned interim analysis. After review of the data, the IDMC will provide advice on continuation of the study, amendment to the protocol, or discontinuation of the study. The final decision will be made by the Sponsor. The procedures on management of the IDMC will be specified in 1 separate IDMC constitutional document.

11 References

1. Pickens A, Orringer MB. Geographical distribution and racial disparity in esophageal cancer. Ann Thorac Surg. 2003;76:S1367-9.
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115-32.
3. Liang H, Fan JH, Qiao YL. Epidemiology, etiology, and prevention of esophageal squamous cell carcinoma in China. Cancer Biol Med. 2017;14(1):33-41.
4. Engel LS, Chow WH, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst. 2003;95:1404-13.
5. Kojima T, Doi T. Immunotherapy for esophageal squamous cell carcinoma. Curr Oncol Rep. 2017;19(5):33.
6. Lai X, Zheng X, Mao W. Research progress in targeted therapy for esophageal cancer. J Chinese Oncol. 2015;21(2):142-50.
7. Sunshine J, Taube JM. PD-1/PD-L1 inhibitors. Curr Opin Pharmacol. 2015;23:32-8.
8. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol. 2015;33(17):1974-82.
9. Doi T, Piha-Paul SA, Jalal SI, et al. Updated results for the advanced esophageal carcinoma cohort of the phase Ib KEYNOTE-028 study of pembrolizumab (MK-3475). 2016 Gastrointestinal Cancers Symposium, Poster Session A Board #F7.
10. Tanaka T, Nakamura J, Noshiro H. Promising immunotherapies for esophageal cancer. Expert Opin Biol Ther. 2017;17(6):723-33.
11. Le DT, Bendell JC, Calvo E, et al. Safety and activity of nivolumab monotherapy in advanced and metastatic (A/M) gastric or gastroesophageal junction cancer (GC/GEC): Results from the CheckMate-032 study. J Clin Onco. 2016;54(1):59-68.
12. Kojima T, Hara H, Yamaguchi K, et al. Phase II study of nivolumab (ONO-4538/BMS-936558) in patients with esophageal cancer: Preliminary report of overall survival. J Clin Oncol. 2016;34(suppl 4S; abstr TPS175).
13. Investigator Brochure for Toripalimab (03 July 2017). Shanghai Junshi Biosciences Co., Ltd..
14. Guidance for Nonclinical Safety Evaluation of Biological Products for Therapeutic Use. National Center for Drug Evaluation, China. January 2001.
15. Standards for Quality Control of Drug Clinical Trials. China Food and Drug Administration. 06 August 2003.
16. Merritt RE, Mahtabifard A, Yamada RE, Crystal RG, Korst RJ. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumor immunity in poorly immunogenic murine lung cancer. J Thorac Cardiovasc Surg. 2003;126:1609-17.
17. Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, Criollo A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med. 2007;13:1050-9.

18. Zhang X, Shen L, Li J, Li Y, Li J, Jin M. A phase II trial of paclitaxel and cisplatin in patients with advanced squamous-cell carcinoma of the esophagus. Am J Clin Oncol. 2008;31(1):29-33.

19. Chaofeng Tang, Yueqin Ma, et al Observation on the treatment of 102 patients with advanced esophageal cancer with paclitaxel combined with cisplatin. Medi Innov China. 2011;08(1):160-1.

20. Liu Y, Ren Z, Yuan L, Xu S, Yao Z, Qiao L, et al. Paclitaxel plus cisplatin vs. 5-fluorouracil plus cisplatin as first-line treatment for patients with advanced squamous cell esophageal cancer. Am J Cancer Res. 2016;6(10):2345-50.

21. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. May 2007.

22. European Medicines Agency Guideline on the Evaluation of Anticancer Medicinal Products in Man EMA/CHPM/205/95/Rev.4. December 2012.

23. Ellis LM, Bernstein D, Voest EE, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014;32(12):1277.

24. Temel J S, Greer J A, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. Chinese J Lung Cancer. 2010;363(9):733-42.

25. Miller V A, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): A phase 2b/3 randomised trial. Lancet Oncology. 2012;13(5):528.

26. Hales R K, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. Ann Oncol 2010;21(10):1944.

27. Emens LA, Braiteh FS, Cassier P, et al. Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer [abstract]. San Antonio Breast Cancer Symposium 2014:PD1-6.

28. Hyde L, Hyde CI. Clinical manifestations of lung cancer. Chest. 1974;65:299-306.

29. Hopwood P, Stephens RJ. Symptoms at presentation for treatment in patients with lung cancer: implications for evaluation of palliative treatment. The Medical Research Council (MRC) Lung Cancer Working Party. Br J Cancer. 1995;71:633-6.

30. Sarna L, Evangelista L, Tashkin D, Padilla G, Holmes C, Brecht ML, et al. Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer. Chest. 2004;125:439-45.

31. Vickery CW, Blazeby JM, Conroy T, Arraras J, Sezer O, Koller M, et al. Development of an EORTC disease-specific quality of life module for use in patients with gastric cancer. Eur J Cancer. 2001;37(8):966-71.

32. Horn L, Spigel DR, Gettinger SN, Antonia SJ, Gordon MS, Herbst RS, et al. Clinical activity, safety and predictive biomarkers of the engineered antibody MPDL3280A (anti-PDL1) in non-small cell lung cancer (NSCLC): Update from a phase Ia study. J Clin Oncology. 2015;33:abstract 8029.

33. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. Jnci Journal of the National Cancer Institute. 1993;85(5):365-76.

34. Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer, 1999;35(6):939.

35. Blazeby JM Gettinger SN, Kowanetz M, Soria JC, et al. Molecular correlates of PD-L1 status and predictive biomarkers in patients with non-small cell lung cancer (NSCLC) treated with the anti-PDL1 antibody MPDL3280A [abstract]. International Association for the Study of Lung Cancer 15th World Conference 2013:MO19.09.

36. Conroy T, Hammerlid E, et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. Eur J Cancer. 2004, 40(15):2260.

37. Di G A, Biagioli M, Maio M. The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. Semin Oncol. 2010, 37(5):499-507.

38. Adverse reactions of ototoxicity to platinol (generic name: cisplatin). http://www.drugs.com/pro/platinol.html. Accessed on 28 October 2017.

39. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

40. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonized. Integrated Addendum to ICH E6(R2): Guideline for Good Clinical Practice E6(R2). 09 November2016.

41. Chen L, Li F. Chromosome aberrations in esophageal cancer and progress in research methods. World Chinese J Digestol. 2006;14(19):1895-9.

42. Xiaoxia H, Ji WM, Shibo L,Weihong X, Xianfu W Yuanyuan L, Ji-Yun L Amplification and overexpression of CTTN and CCND1 at chromosome 11q13 in esophagus squamous cell carcinoma (ESCC) of North Eastern Chinese Population. Int J Med Sci. 2016;13(11):868-74.

43. Pablo Ramos-García, Isabel Ruiz-Ávila, José Antonio Gil-Montoya, Ángela Ayén, Lucía González-Ruiz, Francisco José Navarro-Triviño, Miguel Ángel González-Moles. Relevance of chromosomal band 11q13 in oral carcinogenesis: An update of current knowledge. Oral Oncol. 2017;72:7-16.

44. Hao JJ, Shi ZZ, Zhao ZX, et al. Characterization of genetic rearrangements in esophageal squamous carcinoma cell lines by a combination of M-FISH and array-CGH: Further confirmation of some split genomic regions in primary tumors. BMC Cancer. 2012;12:367.

45. Mosteller RD, et al. N Engl J Med. 1987 Oct 22;317(17):1098

Appendix 1 Schedule of Assessments

Study Assessment	Screening period[a]		All treatment cycles					Unscheduled visit[b]	End of treatment[c]	Survival follow-up[d]
			Induction period			Maintenance period				
Study Day (window)	-28 to -1	-7 to -1	C1D1	C2D1 (±3)	C3-C6D1 (±3)	C7D1 (±3)	From C8D1 to last does of study drug (±3)	NA		
Informed consent signed	x[e]									
Demographic data	x									
Medical history at baseline	x									
Patient-reported outcome[f]			X	x	x	x	x			
Vital signs[g]		x	X	x	x	x	x	x	X	
Body weight		x		x	x				X	
ECOG performance status		x	X	x	x	x	x	x	X	
Body height		x								
ECG[h1]	x				x	x	x		X	
Echocardiography[h2]	x				x		x			
Complete physical examination[i]	x									
Brief physical examination[j]			x	x	x	x	x		x	
Hematology[k]		x		x	x	x	x		x	
Blood biochemistry[l]		x		x	x	x	x		x	
Pregnancy test[m]		x							x	
Coagulation examination (INR, prothrombin time, activated partial thromboplastin time)[n]		x			x	x			x	

Study Assessment	Screening period[a]		All treatment cycles						End of treatment[c]	Survival follow-up[d]
			Induction period			Maintenance period		Unscheduled visit[b]		
Study Day (window)	-28 to -1	-7 to -1	C1D1	C2D1 (±3)	C3-C6D1 (±3)	C7D1 (±3)	From C8D1 to last does of study drug (±3)	NA		
Thyroid function test (TSH, free T3, and free T4)[n]	x				x	x			x	
Urinalysis[o]		x		x	x	x	x		x	
HIV, HBV, and HCV serology[p]	x									
Administration of the investigational drug			x	x	x	x	x			
Tumor response assessments	x[q]				x[r]	x[r]			x[r]	
Serum samples for ADA/trough concentration[s]			x		x	x			x	
Blood samples for biomarkers[t]			x		x	x				
Concomitant medications[u]	x		x	x	x	x	x	x	x	x
Adverse events[v]	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; AE = adverse events; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; CNS = central nervous system; CT = computerized tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; HBV = hepatitis B virus; HbsAG = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NA = not applicable; PD = progression of disease; PRO = patient-reported outcome; SAE = serious adverse event; TSH = thyroid stimulating hormone; T3 = total triiodothyronine.

Note: Unless otherwise specified, all the scheduled visits must be completed within 28 days. During treatment, all the assessments must be conducted prior to administration of the investigational drug, unless otherwise specified.

A Results from the tests or examinations conducted prior to obtaining signed informed consent and within 28 days before Cycle 1 Day 1 may be used; such tests or examination need not be repeated.

B Visits not specified in the trial protocol. They should be conducted when clinically indicated.

C Patients completing the treatment period should return to the research site and complete the end-of-treatment visit within 30 days after the last dose of study drug. The patients permanently terminating the study drug should return to the research site and complete the end-of-treatment visit within 30 days after the last dose of study drug. A visit in which the tumor evaluation

shows progression of disease may be considered as the end-of-treatment visit. If the study drug is terminated due to a delay of study drug administration and a subsequent decision is made that study drug cannot be resumed and the interval from the last dose of study drug infusion to the decision for termination of study drug treatment may be close or more than 30 days, the investigator should complete the end-of-treatment visit as far as possible after the patient confirms the termination of the investigational therapy.

D After end of study drug dosing (using the date of the last dose as starting point), follow-up information will be collected once per month (±7 days) via telephone and/or clinic visit, until death, lost to follow-up, or termination of the study by the Sponsor.

E All signatures on the informed consent must be obtained prior to the conduct of any study-specific procedures.

F The patient should complete the EORTC QLQ C30 and QLQ-OES18 questionnaires prior to receiving any information for tumor status, any non-PRO assessment, and administration of the investigational therapy.

G Including patients' respiratory rate, pulse rate, systolic blood pressure, and diastolic blood pressure, as well as body temperature. Baseline abnormalities are recorded in eCRF for General History and Baseline Diseases. In subsequent visits, any new or aggravated, clinically significant abnormality should be recorded in the Adverse Events page in the eCRF.

H1 A 12-lead ECG is conducted at screening and once every 2 cycles after C1D1 and at the end of treatment visit. During the study, the same instrument should be used as far as possible for ECG. The position of leads should be consistent as far as possible. ECG must be conducted after the patient rests in the supine position for at least 10 minutes.

H2 Echocardiography is conducted at screening and once every 4 cycles after C1D1 to examine left ventricular ejection fraction.

I Including assessments of the head, eyes, ear, nose, and throat, as well as of cardiovascular, skin, musculoskeletal, respiratory, gastrointestinal, urogenital, and nervous systems. Baseline abnormalities are recorded in the eCRF pages titled General History and Baseline Diseases. In subsequent visits, any new or aggravated, clinically significant abnormality should be recorded in the CRF page titled Adverse Events.

J Some examinations are conducted based on the symptoms, as indicated clinically at specified timepoints or as indicated clinically. Any new or aggravated, clinically significant abnormality should be recorded in the eCRF titled Adverse Events.

K Hematology tests involve complete blood counts that include white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, and white blood cell differential counts (neutrophils, eosinophils, basophils, monocytes, and lymphocytes). Results for whole blood count must be available before start of infusion (after C1, samples must have been obtained within 3 days prior to the infusion).

L Blood biochemistry (serum or plasma), including glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein and albumin, serum creatine kinase, and serum creatine kinase isoenzymes. Results for blood biochemistry must be available before start of infusion (after C1, samples must have been obtained within 3 days prior to the infusion).

M At screening, all women of childbearing potential, including those who have undergone a bilateral tubal ligation, must receive a serum pregnancy test and subsequent test per patients' condition.

N The results for coagulation test (INR, PT, and aPTT) and thyroid function test (TSH, free T3, and free T4) are collected at screening, and once per 2 cycles after C1D1 (after C1, the samples must be obtained within 3 days prior to infusion), and at the end-of-treatment visit.

O Urinalysis includes urine pH, specific gravity, glucose, protein, ketone bodies, occult blood, red blood cells, and white blood cells (after C1, samples must be obtained within 3 days prior to infusion).

P Prior to enrollment into the study, all the patients must undergo testing for HBV serology and HCV and HIV tests. HBV serology includes HbsAg, anti-HbsAg antibody, and hepatitis B core antibody [anti-HBc]. Patients who are HCV seropositive and/or HIV seropositive are not eligible for this study. In patients who are HbsAg positive or have a prior history of hepatitis B infection, then an HBV DNA test should be conducted prior to randomization.

Q At screening, a contrast-enhanced CT or MRI scans of the neck, chest, abdomen, and pelvic cavity must be performed (a plain scan may be adopted if the patients are allergic to the contrast medium). At screening, enhanced CT or MRI scan of the head must be conducted to evaluate CNS metastasis in all patients. If CT scan results are unclear, then brain MRI scan must be conducted to confirm or rule out CNS metastasis.

R Whether treatment delay occurs or not, tumor assessment evaluation is conducted once every 6 weeks (±7 days, approximately once per 2 cycles) in the first 12 months after Cycle 1 Day 1, and thereafter once every 9 weeks (±7 days) until progression of disease, loss of clinical benefit, withdrawal of the consent to remain on study, loss to follow-up, death, termination of the

study by the Sponsor, or start of a new antitumor therapy, whichever occurs first. If progression of disease is suspected, then CT scan may be repeated at any time; if a patient withdraws from the investigational therapy for any reason, an imaging examination must be conducted as soon as possible. If the previous tumor evaluation is within 28 days of the date of withdrawal from the study, then it would not need to be repeated. The same imaging modality (CT or MRI), including scanning layer thickness and contrast medium, should be used consistently during the study.

s For the detailed plan, see 0.

t For the detailed plan, see 0.

u Including all drugs/concomitant therapies used in patients from 28 days prior to administration of the investigational drug to the end-of-treatment visit. After the end-of-treatment visit, concomitant medication/concomitant therapies for treatment of AEs/SAEs should also be collected.

v All serious adverse events that occur After obtaining the signed informed consent but prior to the first dose of study drug, should be captured on the CRF. All adverse events occurring after the first dose of study drug through 60 days after the last dose of study drug or start of a new antitumor therapy (whichever occurs first), should be captured on the CRF. After this period, the Sponsor should be notified of any serious adverse event considered to be related to the study drug by the investigator (see Section 0). The investigator should follow up on all the adverse events, until the adverse event has resolved to baseline, becomes stable per the investigator, patient is lost to follow-up, or patient's withdraw informed consent form (whichever occurs first). Every effort should be made to follow up on all the serious adverse events that are considered to be related to the study drug or study-related procedures until the final outcome can be reported.

Appendix 2 Schedule of Biomarkers and Anti-drug Antibody Sampling

Visit	Timepoint	Sample type	Volume of whole blood collected
Screening period (Days -28 to -1)	NA	Tumor tissue specimens (if possible, paraffin block or 8 FFPE sections are preferable) Fresh or archived tissues may be acceptable	NA
Day 1 of every 2 cycles from Cycle 1 in the 1st year	Prior to administration (administration date of the investigational drug)	Toripalimab ADA/trough concentration	3 mL
	Prior to administration (administration date of the investigational drug)	Biomarkers	10 mL
Day 1 of every 6 cycles after the 1st year	Prior to administration (administration date of the investigational drug)	Toripalimab ADA/trough concentration	3 mL
	Prior to administration (administration date of the investigational drug)	Biomarkers	10 mL
Fresh biopsy (during treatment or at progression, including follow-up period)	NA	Tumor tissue specimen	NA
First progression of disease	NA	Biomarkers	10 ml
End of treatment	NA	Toripalimab ADA/trough concentration	3 ml

ADA = anti-drug antibody; FFPE = formalin-fixated paraffin embedded; NA = not applicable.

Appendix 3 Esophageal Cancer Staging of the American Joint Committee on Cancer, v8 (2017)

Cancer staging categories for Squamous Cell cancer of the Esophagus and Esophagogastric junction

T category

- Tx - The primary tumor cannot be determined
- T0 - No evidence for primary tumor
- Tis – High-grade dysplasia, defined as malignant cells confined by the basement membrane
- T1 - Tumor invades the lamina propria, muscularis mucosae or submucosa
  - T1a - Tumor invades the lamina propria or muscularis mucosa
  - T1b - Tumor invades the submucosa
- T2 - Tumor invades the esophageal muscularis propria
- T3 - Tumor invades the adventitia
- T4 - Tumor invades adjacent structures
  - T4a - Tumor invades the pleura, peritoneum, pericardium, or diaphragm
  - T4b - Tumor invades other adjacent structures, e.g., aorta, trachea, or vertebral body

N – Category

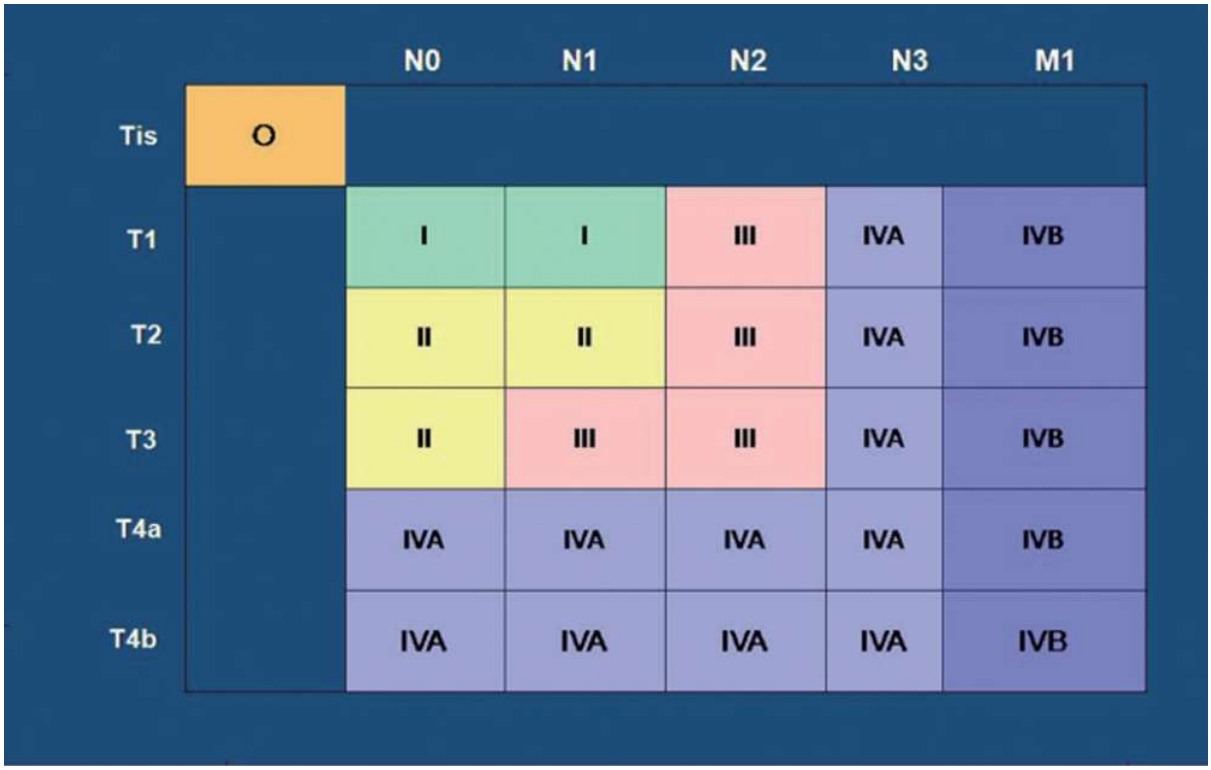
- Nx - Regional lymph node metastasis cannot be assessed
- N0 – No regional lymph node metastases
- N1 - Metastasis to 1 to 2 regional lymph nodes
- N2 - Metastasis to 3 to 6 regional lymph nodes
- N3 - Metastasis to ≥7 regional lymph nodes

M Category

- M0 - No distant metastasis
- M1 - Distant metastasis

Squamous cell carcinoma G category

- Gx - Differentiation cannot be assessed
- G1 – Well-differentiated
- G2 - Moderately differentiated.
- G3 - Poorly differentiated.



AJCC v8, Staging of Squamous Cell Cancer.Esophageal Cancer

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST)

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

Please refer to: http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf.

Appendix 5 Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

Objective

AIM: RECIST 1.1 has its shortcomings for targeted immunotherapy in oncology. Using RECIST 1.1 in immunotherapy trials would lead to declaration of progressive disease (PD) too early, when the treatment effect is not yet fully evident. RECIST also neglects the importance of the 'flare effect' -pseudo-progression effect within the so-called flare time window.

Immune related Response Criteria (irRC) based on WHO criteria were published with an aim to provide better assessment of the effect of immunotherapeutic agents. With this poster we introduce irRECIST based on RECIST 1.1, irRC and Nishino et al., 2013 findings. Our aim is to define criteria that better capture antitumor activity and reduce irRC criteria ambiguity.

Consistent implementation of irRECIST by both investigators and blinded independent readers will help reduce site: central discordance.

METHODS: The adaptations from irRC and WHO criteria, as applicable in immunotherapy clinical studies, are documented in the "irRECIST Modifications and Clarifications" column in a comparative table format within our Blinded Independent Central Review (BICR) Charter.

The modifications we introduce represent adaptations of published criteria based on radiology practice and clinical trial experience, and they provide more objective and reproducible response assessments for investigators and for the central independent image review.

RESULTS: irRECIST criteria are based on irRC criteria adapted for unidimensional measurements, as outlined in Nishino et al., 2013. To further align the criteria with RECIST 1.1 we outline the approach for the assessment of baseline selected non-target lesions and new non-measurable lesions, and discuss the impact of those lesions on the overall tumor response assessment.

Guidelines for the evaluation of patients with non-target disease only and patients in adjuvant setting is provided.

Original irRC, Including WHO Criteria References	irRECIST Modifications and Clarifications	Rationale for Modification
At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.	**1. 0 Baseline: Measurable Lesion Definitions and Target Lesion Selection** Follow the definitions from RECIST 1.1. Measurable lesions must be accurately measured in at least one dimension with a minimum size of: • 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis for nodal lesions • 10 mm caliper measurement by clinical exam • 20 mm by chest X-ray	Up to 5 target lesions may be selected at baseline. Lesions will be measured unidimensionally. The minimum target lesion size at baseline in irRECIST is aligned with RECIST 1.1, as outlined in Nishino et al., 2013.
WHO 5.1.2 Unmeasurable Disease There are many forms of unmeasurable disease, and only a few are mentioned as examples: Lymphangitic pulmonary metastases. Skin involvement in breast cancer. Abdominal masses that can be palpated but not measured.	**1.1. Baseline: Non-measurable Lesion Definitions** Follow the definitions from RECIST 1.1 Non-target lesions will include: • Measurable lesions not selected as target lesions • All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), ie. the longest per-pendicular diameter is ≥10 and < 15 mm. • Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.	Although irRC does not specifically define non-target lesions, irRC is derived from WHO criteria and indicates accordance with the same for the purposes of definitions of non-target lesions. Further clarifications in alignment with RECIST 1.1 are provided.
Not specified.	**1.2 Baseline: Target and Non-Target Lymph Node Lesion Definitions** Follow the definitions from RECIST 1.1	No change in definition of target and non-target lymph nodes from RECIST 1.1.
Not specified.	**1.3 Baseline: Non-Target Lesion Selection** All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline.	In alignment with RECIST 1.1, all malignant lesions have to be selected at baseline. The excess of measurable lesions and all true non-measurable lesions will be selected as non-target lesions at baseline and followed at subsequent timepoints.
Not specified.	**1.4 Baseline: Bone Lesions** Follow the definitions from RECIST 1.1. Regardless of the imaging modality blastic bone lesions will not be select-ed as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.	Bone lesions are to be handled the same as in RECIST 1.1.
Not specified.	**1.5 Baseline: Brain Lesions** detected on brain scans can be considered as both target or non-target lesions.	Brain lesions can be selected as target or non-target lesions at baseline, depending on the protocol definition, indication, and study design.

Original irRC, Including WHO Criteria References	irRECIST Modifications and Clarifications	Rationale for Modification
Not specified.	**1.6 Baseline: Cystic and Necrotic Lesions as Target Lesions** Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.	RECIST 1.1 does not integrate viability of tumor tissue into the assessment, and that is carried over into irRECIST.
Not specified.	**1.7 Baseline: Lesions With Prior Local Treatment** During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.	In order to minimize site vs. central discrepancy information about prior intervention needs to be available to both the investigators and independent reviewers.
Not specified.	**1.8 Baseline: No Disease at Baseline** If a patient has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up timepoints unless new measurable lesions are identified and contribute to the TMTB.	irND is a valid assessment in studies with adjuvant setting where the protocol and study design allow to include patients with no visible disease. This had not been addressed at all in any prior immune-response related criteria but needs to be included to also allow for these patients to be assessed accurately.
At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5×5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden: **SPDindex lesions + SPDnew measured lesion**	**2.0 Follow-up: Recording of Target and New Measureable Lesion Measurements** The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up.	In alignment with Nishino et al., 2013, unidimensional measurements are used. Measurements of all measured lesions (baseline-selected target lesions and new measurble lesions) are combined into TMTB at follow-up.
	2.1 Follow-up: Definition of Measurable New Lesions In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.	Proposed selection of up to 5 new measurable lesions of at least 10 mm each verus 10 new measurable lesions as suggested in the irRC criteria is due to the following: 5 new measurable lesions add up at least 50 mm to the TMTB. Since PD is determined by at least a 20% increase in TMTB compared to nadir, this would mean that for irPD assessment the nadir TMTB had to be 25 cm, or 10 cm for 2 lesions in one organ, which is a significant tumor burden already for any cancer patient. That is why measuring up to 5 new lesions in total is sufficient and will not obstruct an irPD assessment. Measuring more than 5 new lesons is not needed. Larger lesions must be preferred as new measurable over smaller lesions, because there will be a greater impact of the TMTB %-increase by these larger lesions for irPD, to support a most conservative approach.

Original irRC, Including WHO Criteria References	irRECIST Modifications and Clarifications	Rationale for Modification
Non-index lesions at follow-up timepoints contribute to defining irCR (complete disappearance required).	**2.2 Follow-up: Non-Target Lesion Assessment** The RECIST 1.1 definitions for the assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.	Non-target lesions have a subordinate function. In the event that non-target lesions massively progress one cannot ignore such worsening and in these rare cases irPD based only on non-target lesions will be a valid assessment option.
New, non-measurable lesions at follow-up timepoints do not define progression, they only preclude irCR.	**2.3 Follow-up: New Non-Measurable Lesions Definition and Assessment** All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new non-measurable lesions prevent irCR.	When new non-measurable lesions substantially worsen in these rare cases irPD based only on new non-measurable lesions will be an assessment option.
irRC Overall Tumor Assessments **irCR**, complete disappearance of all lesions (whether measurable or not, and no new lesions) • Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented **irPR**, decrease in tumor burden >50% relative to baseline • Confirmed by a consecutive assessment at least 4 weeks after first documentation **irSD**, not meeting criteria for irCR or irPR, in absence of irPD **irPD**, increase in tumor burden >25% relative to nadir (minimum recorded tumor burden) • Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented	**2.4 irRC Overall Tumor Assessments** **irCR,** complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory. **irPR**, decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions. **irSD**, failure to meet criteria for irCR or irPR in the absence of irPD. **irNN**, no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD. **irPD**, minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. **irNE**, used in exceptional cases where insufficient data exists. **irND**, in adjuvant setting when no disease is detected.	The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions. The thresholds for irPR and irPD assessment are aligned with RECIST 1.1, and confirmation of response is not required. An irPD confirmation scan may be recommended for patients with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response.

CONCLUSIONS: irRECIST criteria as outlined here introduce the needed clarifications and adjustments to irRC criteria and Nishino et al., 2013 publication to allow for treatment

evaluations that better meet both investigators' and patients' needs and with that better reflect sponsors' demands for more reliable and reproducible study data in targeted immunotherapy in oncology studies. The main adaptation of the existing immune-response criteira lies in the assessment of all detected lesions. Unequivocal and substantial increase of non-target and new non-measurable lesions prevents irCR and may also lead to irPD. Reduction of the tumor burden in patients in an adjuvant setting may lead to irPR and such patients may therefore be enrolled in studies with response endpoints. Clinical relevance of these adaptations needs to be confirmed.

SUMMARY AND ADDITIONAL GUIDANCES

1. TMTB: Baseline-selected target lesions and new measurable lesions should NOT be assessed separately. Measurements of those lesions should be combined into the Total Measured Tumor Burden (TMTB), and one combined assessment provided.
2. New Measurable Lesions: According to irRC a measurable new lesion has to be at least 5 mm x 5 mm to be selected as an index lesion. For bidimensional measurements this threshold was acceptable. In irRECIST, criteria for unidimensional lesion measurement apply to both target and new measurable lesions: a minimum 10 mm in the longest diameter for non-nodal lesions, and a minimum 15 mm in short axis for lymph nodes. Smaller lesions contribute to the non-target or new non- measurable tumor burden, but do not get measured.
3. irPR if no Target Lesions: If new measurable lesions appear in patients with no target lesions at baseline, irPD will be assessed. That irPD timepoint will be considered a new baseline, and all subsequent timepoints will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation.
4. irPR in Adjuvant Studies: irRECIST can be used in the adjuvant setting, in patients with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These patients can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response.

Considering 3 and 4, sponsors may consider enrolling patients with no measurable disease and/or patients with no visible disease at all in studies with response related endpoints.

5. Non-Target Lesions: In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent timepoints and become measurable. Only true new lesions can be measured and contribute to the TMTB.

6. Example: A patient has multiple lung metastases, all smaller than 10 mm and selected as non-target lesions at baseline. If, at a subsequent timepoint some of these non-target lesions increase and become > 10 mm, and one new lesion >10 mm appears, only the new measurable lesion will contribute to the TMTB, and not the baseline selected non-target lesion that increased in size. Otherwise, such an increase would make persisting non-target lesions switch into the new measurable lesion category which would be inaccurate, as the lesion existed at baseline.
7. irPD Based on Non-Target Lesions: Unlike irRC that neglect non-target lesions for the assessment of irPD, in irRECIST a substantial and unequivocal increase of non-target lesions is indicative of progression.
8. irPD Based on New Non-Measurable Lesions: According to irRC, a patient with multiple new lesions of 9 mm would be considered non-PD, whereas a patient with just one new lesion of 10 mm may be assessed as irPD if the TMTB of such a patient increases ≥ 20% compared to nadir. According to irRECIST, the reviewer may assign irPD for the patient with multiple new lesions of 9 mm if they are considered to be a sign of unequivocal, massive worsening (see 2.3)
9. irPD Confirmation: Progression confirmation no less than 4 weeks after the initial irPD assessment is recommended especially in case of marginal disease growth and if the first irPD assessment is within the compound-specific tumor flare window.

REFERENCES

1. JD Wolchok, A Hoos, O Bohnsack, et.al., Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria, Clin Cancer Res 2009;15(23) December 1, 2009
2. Nishino M et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013 Jul 15;19(14):3936-43
3. Therasse P, Arbuck SG, et al.: New Guidelines to Evaluate the Response to Treatment in Solid Tumors. Journal of the National Cancer Institute 2000 92(3):205-216]
4. Eisenhauer EA, Therasse P, Bogaerts J, et al.: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). In: Eur. J. Cancer. 45, Nr. 2, Januar 2009, S. 228–47.
5. Therasse P, Eisenhauer EA, Verweij J: RECIST revisited: a review of validation studies on tumour assessment. In: Eur. J. Cancer. 42, Nr. 8, Mai 2006, S. 1031–9.

6. WHO handbook for reporting results of cancer treatment. Geneva (Switzerland): World Health Organization Offset Publication No. 48; 1979.

[Source: https://www.parexel.com/application/files_previous/7914/2186/7838/irrecist-path-PDF.pdf]

Appendix 6 Recommendations for Treatment of Hypothyroidism

Levothyroxine sodium (common brandname: Euthyrox) is recommended for patients who develop drug-related hypothyroidism.

The dose of levothyroxine sodium recommended in this appendix is a general recommendation; a patient's daily dose should be determined from the results of laboratory tests and clinical examinations. As total thyroxine and thyroxine free levels in many patients would be increased, the baseline concentration of serum thyroid stimulating hormone (TSH) is a reliable basis to determine a therapeutic method. Generally, thyroid hormone replacement therapy should be started at a low dose and increased gradually in dose every 2 to 4 weeks until the replacement dose is sufficient. Generally speaking, patients with hypothyroidism requires a lifelong oral administration of the drug.

Special attention should be exercised in the initiation phase of thyroid hormone replacement therapy in elderly patients or patients with coronary heart disease or chronic hypothyroidism. A low initial dose (such as 12.5 μg/d) should be selected, and the oral dose should be increased slowly (such as increase of 12.5 μg/d every 2 weeks).

If the maintenance dose is lower than the optimal dose, then hypothyroidism cannot be corrected completely based on TSH level.

Clinical experience has demonstrated that a low dose of levothyroxine is effective for patients with a low body weight or patients with macronodular goiter.

Levothyroxine sodium should be taken under a fasted state (e.g., half an hour prior to breakfast) as a single daily dose with an adequate amount of liquid (such as half glass of water).

List of Recommended Doses

	Dose	**50 μg tablets**	**100 μg tablets**	**Administration frequency**
Initial dose (After the initial dose, increase the dose by 25-50 μg per day, every 2-4 weeks, until the maintenance dose is reached)	25～50 μg	½~1 tablet	¼~½ tablet	QD
Maintenance dose	100～200 μg	2~4 tablets	1~2 tablets	QD

Confirm the cause of secondary hypothyroidism prior to initiation of treatment. Glucocorticoids should be administered as necessary. Once the levothyroxine maintenance dose is determined, adjust the thyroid hormone replacement dose based on the patient's clinical responses and laboratory test results or if the patient is switched to another thyroid hormone replacement drug.

For details, please refer to the package insert of the respective thyroid hormone replacement product.

Appendix 7 EORTC QLQ-C30 Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

	Not at all	A little	Quite big	Very big
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you have to stay in bed or a chair during the day?	**1**	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not at all**	**A little**	**Quite big**	**Very big**
6. Were you limited in doing either your work or other daily activities?	1	2	*3*	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	**1**	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

table continues on next page…

Appendix 7 - EORTC QLQ-C30 Questionnaire (continued)

English

During the past week:	Not at all	A little	Quite big	Very big
17. Have you had diarrhea?	1	**2**	3	4
18. Were you tired?	1	**2**	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things like reading a newspaper or watching television?	1	2	**3**	4
21. Did you feel tense?	1	**2**	3	4
22. Did you worry?	1	**2**	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	**2**	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	**2**	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	**2**	3	4

For the following questions, please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health condition in the past week?

1	2	3	4	5	6	*7*
Very poor						Excellent

30. How would you rate your overall quality of life in the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 8 EORTC QLQ-OES18 Questionnaire

EORTC Quality of Life Questionnaire, **QLQ-OES18**

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

In the past 1 week:	**Not at all**	**Some what**	**Quite**	**Very**
31. Could you eat solid food?	1	2	3	4
32. Could you eat liquid or semiliquid food?	1	2	3	4
33. Could you drink liquids?	1	2	3	4
34. Have you had trouble with swallowing your saliva?	1	2	3	4
35. Have you choked when swallowing?	1	2	3	4
36. Have you had trouble enjoying your meals?	1	2	3	4
37. Have you felt full up too quickly?	1	2	3	4
38. Have you had trouble with eating?	1	2	3	4
39. Have you had trouble with eating in front of other people?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Did food and drink taste different from usual?	1	2	3	4
42. Have you had trouble with coughing?	1	2	3	4
43. Have you had trouble with talking?	1	2	3	4
44. Have you had acid indigestion or heartburn?	1	2	3	4
45. Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
46. Have you had pain when you eat?	1	2	3	4
47. Have you had pain in your chest?	1	2	3	4
48. Have you had pain in your stomach?	1	2	3	4

Appendix 9 Eastern Cooperative Oncology Group Performance Status

Score	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, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

Appendix 10 Management of Allergic Reactions

Required Equipment

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous injection, intravenous injection, and/or tracheal administration according to the standard practices for treatment
- Antihistamine agents
- Corticosteroids
- Solution for intravenous infusion, infusion tube, catheter, and adhesive tape

Procedures

In cases of suspected allergic reactions occurred during infusion of the investigational drug, the following procedures should be implemented:

- Discontinue the study drug infusion
- Use a tourniquet at the proximal end of the injection site to delay systemic absorption of the study drug; do not occlude arterial blood stream of affected limbs
- Maintain airway patency
- Administer antihistamine, epinephrine, or other drugs, as directed by the doctor on duty
- Maintain patient under continued observation and record observations

Appendix 11 Listing of Autoimmune or Immunodeficiency Disorders to be Considered During Screening

Carefully inquire regarding the patient's history of acquired or congenital immunodeficiency or autoimmune disease. Patients with a history of immunodeficiency or autoimmune disease, as listed in the table below, are ineligible for enrollment into the study. The possible exception to this exclusion criteria is patients with a history of atopic disease or childhood arthritis, in which the clinical likelihood of exacerbation of autoimmune disease is low. The patients with a history of autoimmune-related hypothyroidism who are receiving a stable dose of thyroid hormone can be enrolled in the study. In addition, transient autoimmune manifestations of acute infectious diseases that are relieved during treatment for infectious pathogens (for example, acute Lyme arthritis) are not excluded. For any uncertainty regarding the autoimmune disease exclusion criteria, please contact the medical monitor.

Autoimmune Disease and Immunodeficiency

Acute disseminated encephalomyelitis	Acquired epidermolysis bullosa	Ord's thyroiditis
Addison disease	Gestational pemphigoid	Pemphigus
Ankylosing spondylitis	Giant cell arteritis	Pernicious anemia
Antiphospholipid antibody syndrome	Goodpasture syndrome	Polyarteritis nodosum
Aplastic anemia	Graves' disease	Arthritis
Autoimmune hemolytic anemia	Guillain-Barre syndrome	Polyglandular autoimmune syndrome
Hepatitis autoimmune	Hashimoto disease	Primary biliary cirrhosis
Autoimmune hypoparathyroidism	IgA nephropathy	Psoriasis
Autoimmune hypophysitis	Inflammatory bowel disease	Reiter's syndrome
Autoimmune myocarditis	Cystitis interstitial	Rheumatoid arthritis
Autoimmune oophoritis	Kawasaki disease	Sarcoidosis
Autoimmune orchitis	Lambert-Eaton myasthenic syndrome	Dermatosclerosis
Autoimmune thrombocytopenic purpura	Lupus erythematosus	Sjögren syndrome
Behcet's disease	Lyme disease - chronic	Stiff-Person syndrome
Bullous pemphigoid	Meniere syndrome	Aorto-arteritis
Chronic fatigue syndrome	Mooren's ulcer	Ulcerative colitis
Chronic inflammatory demyelinating polyneuropathy	Circumscribed scleroderma	Vitiligo
	Sclerosis multiple	Vogt-Kovanagi-Harada disease
Chung-Strauss syndrome	Myasthenia gravis	Wegener granulomatosis
Crohn disease	Neuromyotonia	

Dermatomyositis	Oculo-cerebello-myoclonic syndrome	
Type 1 diabetes	Neuritis optic	
Familial dysautonomia		