Clinical Study Protocol

Protocol Title:	**A PHASE III, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER, DOUBLE-BLIND STUDY COMPARING TORIPALIMAB INJECTION（JS001） COMBINED WITH CHEMOTHERAPY VERSUS PLACEBO COMBINED WITH CHEMOTHERAPY FOR RECURRENT OR METASTATIC NASOPHARYNGEAL CANCER**
Protocol Number:	**JS001-015-III-NPC**
Test Product:	**Toripalimab Injection (JS001)**
Study Phase:	**Phase III**
Sponsor:	**Shanghai Junshi Biosciences Co., Ltd.** **Floor 13, Building 2, No. 36/58, Haiqu Road, Pudong New Area, Shanghai,200120, P.R.China**
Medical Monitor:	**Weihua Wang, Medical Director**
Principal Investigator:	**Prof. Ruihua Xu**
Version number:	**6.0**
Version date:	**2020-Oct-14**
Previous version:	**1.0 (2018-Mar-02）** **2.0 (2018-Sep-17）** **3.0 (2019-May-28)** **4.0 (2020-May-15)** **4.1 (2020-May-26)** **5.0 (2020-Aug-18)**

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Protocol Approval Form

Signature of Sponsor's Representative

The signatory agrees to the content of the final version of this clinical study protocol.

Name: Wei Liu

Designation: Head of Clinical Medicine

Signature

Oct. 14, 2020

Date

PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE III, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER, DOUBLE-BLIND STUDY COMPARING TORIPALIMAB INJECTION (JS001) COMBINED WITH CHEMOTHERAPY VERSUS PLACEBO COMBINED WITH CHEMOTHERAPY FOR RECURRENT OR METASTATIC NASOPHARYNGEAL CANCER**
PROTOCOL NUMBER:	**JS001-015-III-NPC**
VERSION NUMBER:	**6.0**
TEST PRODUCT:	**Toripalimab Injection (JS001)**
MEDICAL MONITOR:	**Weihua Wang, Medical Director**
SPONSOR:	**Shanghai Junshi Biosciences Co., Ltd**

I agree to conduct the study in accordance with the current protocol.

_____
Principal Investigator's Name (print)

_____ _____
Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy to the contact provided below.

Name _____

Address _____

Protocol synopsis

Name of Sponsor/Company:	Shanghai Junshi Biosciences Co., Ltd.
Test Product:	Toripalimab Injection (JS001 or TAB001)
Name of Active Ingredient:	Recombinant humanized anti-PD-1 monoclonal antibody
Title of Study:	A Phase III, Randomized, Placebo-Controlled, Multicenter, Double-Blind Study Comparing Toripalimab Injection (JS001) Combined with Chemotherapy versus Placebo Combined with Chemotherapy for Recurrent or Metastatic Nasopharyngeal Cancer
Protocol No:	JS001-015-III-NPC
Indication:	Nasopharyngeal Cancer
Primary Investigator:	Prof. Ruihua Xu
Study center(s):	Approximately 40 sites in China mainland, Taiwan, Singapore.
Phase:	III

Objectives:

Primary:

- To evaluate the efficacy of Toripalimab Injection (JS001) plus chemotherapy compared with placebo plus chemotherapy，as measured by independent review committee (IRC)-assessed progression free survival (PFS) according to RECIST v1.1 in all patients.

Secondary:

- To evaluate the efficacy of JS001 plus chemotherapy compared with placebo plus chemotherapy, as measured by overall survival (OS).
- To evaluate the efficacy of JS001 plus chemotherapy compared with placebo plus chemotherapy, as measured by investigator- and IRC-assessed overall response rate (ORR), duration of response (DoR), and disease control rate (DCR) according to RECIST v1.1.
- To evaluate the efficacy of JS001 plus chemotherapy compared with placebo plus chemotherapy, as measured by investigator-assessed PFS according to RECIST v1.1.
- To evaluate the IRC- and investigator-assessed PFS rate at 1 and 2 years in each treatment arm.
- To evaluate the OS rate at 1 and 2 years in each treatment arm.
- To assess disease-related symptoms and health related quality of life (HRQoL) in patients treated with JS001 plus chemotherapy compared with placebo plus chemotherapy using the EORTC QLQ-C30, EORTC QLQ-H&N35 and ECOG performance status assessments.

- To evaluate the safety and tolerability of JS001 plus chemotherapy compared with placebo plus chemotherapy.
- To evaluate the incidence and titers of ADAs against JS001 and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety and efficacy.
- To evaluate the efficacy of JS001 plus chemotherapy compared with placebo plus chemotherapy，as measured by investigator- and IRC-assessed PFS, ORR, DoR and DCR according to irRECIST.

Exploratory:

- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers (including but not limited to PMBC, PD-L1, PD-1, tumor mutation burden and others) in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to JS001.
- To evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumor volume related to the immunomodulatory activity of JS001 (i.e., pseudoprogression and tumor immune infiltration) from true disease progression.

Study design:

This is a randomized, placebo-controlled, multi-center, double blinded, Phase III study to determine the efficacy and safety of Toripalimab Injection (JS001) in combination with gemcitabine/cisplatin compared with placebo in combination with gemcitabine/cisplatin as first-line treatment in patients with histological/cytological confirmation of recurrent or metastatic nasopharyngeal carcinoma (NPC). Patients who fulfill all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio according to the following stratification scheme:

- ECOG performance status (0 versus 1)
- Disease stage (recurrent versus metastatic)

Patients will be randomized in a 1:1 ratio to receive treatment every 3 weeks (Q3W) with JS001 plus gemcitabine/cisplatin (Arm A) or placebo plus gemcitabine/cisplatin chemotherapy (Arm B) in the 'during chemotherapy' phase. During the 'post-chemotherapy' phase, patients randomized to Arm A or Arm B will continue treatment with JS001 or placebo as maintenance therapy Q3W until excessive toxicity or progressive disease, withdrawal of consent or Investigator's judgement or a maximum of 2 years. Patients may continue treatment with JS001 (Arm A) or placebo (Arm B) beyond radiographic progression by the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, provided they are experiencing clinical benefit, as assessed by the Investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression, as determined by the sponsor medical monitor or designee and treating physician after an integrated assessment of radiographic data and clinical status.

Tumor evaluation scans will be performed at screening (as baseline) then every 6weeks in the first 12 months then every 9 weeks thereafter until objective disease progression.

This is a double blinded, one interim efficacy analysis of PFS is planned and pre-defined stopping boundary is set for two-sided p-value. The iDMC will provide the recommendation as to whether to unblind the study or not according to the data of interim analysis and the iDMC charter if the stopping boundary is crossed. If the Sponsor accepted the recommendation and unblind the study, JS001 will be provided to the patients who were randomized to arm A and still on JS001 treatment until the treatment discontinuation criteria are met according to protocol, the placebo treatment will be terminated for the patients who were randomized to arm B. After the

study is unblinded, the tumor evaluation, survival follow-up, safety information, and so on information collection should be performed as required by the protocol.	
Planned number of patients:	Expected median PFS time is about 7 months for standard chemotherapy. With an expected enrollment of 14 months, 280 patients (140 per arm) are needed to observe 200 PFS events at approximately 25 months after the first patient is randomized in order to detect the PFS improvement of HR=0.67 with 80% power at a 2-sided significance level of 0.05, assuming the dropout rate is 5% over 12 months for PFS.
Inclusion criteria:	To be eligible to participate in the study, patients must meet **all** of the following Inclusion Criteria: 1. Age ≥ 18 years and ≤75 years. 2. An archival tumor specimen or fresh tumor biopsy sample is available. 3. Histological/cytological confirmation of NPC. 4. Primarily metastatic (stage IVB as defined by the International Union against Cancer and American Joint Committee on Cancer staging system for NPC, eighth edition) or recurrent NPC after curative treatment, which is not amenable for local regional treatment or curative treatment. No previous systemic chemotherapy was given for metastatic or recurrent disease 5. For the recurrent NPC after curative treatment (including radiotherapy and/or induction, concurrent or adjuvant chemotherapy), the interval between recurrence and the last dose of previous radiotherapy or chemotherapy must be more than 6 months. 6. At least 1 measurable lesion according to RECIST version 1.1. 7. Life expectancy ≥ 3 months. 8. Performance status 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) criteria (Appendix 3). 9. Adequate organ function: • Hematologic: leucocytes ≥ 4.0 × 10^9/L, Absolute Neutrophil Count ≥ 2.0 × 10^9/L, hemoglobin ≥ 90 g/L, and platelets ≥ 100.0 × 10^9/L. • Hepatic: bilirubin ≤ 1.5 × upper limit of normal (ULN)(patients with known Gilbert's disease who have serum bilirubin level ≤ 3 × ULN may be enrolled), AST and ALT ≤ 3 × ULN (AST/ALT ≤ 5 × ULN if liver metastases), with alkaline phosphatase ≤ 3 × ULN (ALP ≤ 5 × ULN if liver or bone metastases); albumin ≥ 3 g/dL;

	• International Normalized Ratio (INR) or Prothrombin Time (PT) or Activated Partial Thromboplastin Time (aPTT) ≤ 1.5 × ULN. • Renal: serum creatinine ≤ 1.5 ULN and creatinine clearance ≥ 60 mL/min according to Cockcroft-Gault formula (Appendix 8) 10. Toxicities from any prior therapy, surgery, or radiotherapy must have resolved to Grade 0 or 1 as per the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE 5.0), excluding any grade alopecia. 11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures. 12. Female patients are eligible to enter and participate in the study if they are of: • Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who o Has had a hysterectomy, o Has had a bilateral oophorectomy (ovariectomy), o Has had a bilateral tubal ligation, or o Is post-menopausal (total cessation of menses for ≥ 1 year). • Childbearing potential, has a negative serum pregnancy test at screening (within 7 days of the first investigational product administration), and uses adequate contraception before study entry and throughout the study until 60 days after the last investigational product administration. Adequate contraception, when used consistently and in accordance with both the product label and the instructions of the physician, are defined as follows: o Any intrauterine device with a documented failure rate of less than 1% per year. o Double barrier contraception defined as condom with spermicidal jelly, foam, suppository, or film; OR diaphragm with spermicide; OR male condom and diaphragm.
Exclusion criteria	Patients will be excluded from the study, if **any** of the following criteria is met: 1. History of severe hypersensitivity reactions to other mAbs or any ingredient of Toripalimab Injection (JS001). 2. Active or untreated CNS metastases (e.g., brain or leptomeningeal), as determined on CT or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments. Patients who have prior therapies for brain or leptomeningeal metastasis and has been stabilized for ≥ 2 months and has discontinued systemic steroids

	therapy (> 10 mg/day prednisone or equivalent) > 4 weeks prior to randomization could be included. 3. Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 2 weeks prior to randomization 4. Patients with necrotic lesions have potential risk of massive hemorrhage at the discretion of investigator. 5. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures Patients with indwelling catheters (e.g., PleurX® catheter) are allowed. 6. Uncontrolled tumor-related pain Patients requiring pain medication must be on a stable regimen at study entry. Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment. Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to enrollment. 7. Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium greater than the ULN) 8. Malignancies other than NPC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated with curative intent, ductal carcinoma in situ treated surgically with curative intent) 9. Prior therapy targeting PD-1 receptor, or its ligand PD-L1, or cytotoxic T-lymphocyte-associated protein 4 (CTLA4) receptor. 10. Use of antineoplastic traditional herbal medicine within 4 weeks before randomization. 11. Major surgical procedure other than for diagnosis of NPC within 28 days prior to randomization or anticipation of need for a major surgical procedure during the study.

	12. History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain -Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 11 for a more comprehensive list of autoimmune diseases) Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study. Patients with controlled Type I diabetes mellitus on a stable insulin regimen are eligible for this study. 13. Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or IL-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to randomization 14. Treatment with systemic corticosteroids (> 10 mg daily prednisone equivalents) or other systemic immunosuppressive medications (including, but not limited to, prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to randomization. Use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids is allowed. Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor. Patients with history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments performed on MRI. The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency is allowed. 15. Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation 16. History of idiopathic pulmonary fibrosis, drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans), idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. 17. History of hypersensitivity to gemcitabine or cisplatin or to any of the excipients.

	18. Use of any live vaccines (e.g., against infectious diseases such as influenza, varicella, etc.) within 4 weeks (28 days) before randomization. 19. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result and HBV DNA detected by study site lab ≥ 1000 cps/mLor the lower limit of the local lab), hepatitis C, or human immunodeficiency virus (positive HIV antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible only if they are negative for HBV DNA (HBV DNA detected by study site lab < 1000 cps/mL or the lower limit of the local lab). Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. 20. Underlying medical conditions with clinical significance (such as dyspnea, pneumonitis, pancreatitis, uncontrollable diabetes, active or uncontrollable infection, drug or alcohol abuse, or psychiatric conditions), which in the Investigator's opinion can affect the administration of study drugs and protocol compliance. 21. Presence of a significant neurological or psychiatric disease, including dementia and seizures. 22. Have NCI-CTCAE ≥ Grade 2 peripheral neuropathy. 23. Female patients who are at pregnancy or lactation. 24. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater, Appendix 6), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
Investigational product, dose, schedule and mode of administration:	Test product: Toripalimab Injection (JS001) JS001 will be administered at the dose of 240 mg Q3W, as an intravenous (IV) infusion over 60 minutes followed by a 60-minute observation period (only required in the first 2 cycles). If no infusion-related reactions have occurred, subsequent infusions will be administered over 30 minutes.

	In the during-chemotherapy phase, JS001 will be given before gemcitabine and cisplatin. After up to 6 cycles of chemotherapy, during the post-chemotherapy phase, JS001 and best supportive care (BSC) can be continued Q3W until excessive toxicity or progressive disease, withdrawal of consent, at the discretion of the Investigator or for a maximum of 2 years.
Reference product, dose, schedule and mode of administration:	Reference product (comparator): matching placebo. Placebo will be administered Q3W, as an IV infusion over 60 minutes followed by a 60-minute observation period (only required in the first 2 cycles). If no infusion-related reactions have occurred, subsequent infusions will be administered over 30 minutes. In the during-chemotherapy phase, the matching placebo will be given before gemcitabine and cisplatin. After up to 6 cycles of chemotherapy, placebo and BSC can be continued Q3W until excessive toxicity or progressive disease, withdrawal of consent, at the discretion of the Investigator or for a maximum of 2 years.
Associated products dose, schedule and mode of administration	Associated products: gemcitabine and cisplatin ***In Arm A & B*:** 60 minutes after the end of Toripalimab Injection (JS001) or placebo infusion (only required in the first 2 cycles), gemcitabine 1000 mg/m²IV over 30 minutes are given on Days 1 & 8, and cisplatin 80 mg/m²IV over 4 hours are given on Day 1 of each cycle. Chemotherapy is given Q3W for up to 6 cycles according to drug label and to local standards for premedication and other prophylactic medications.

Assessment Parameter and Criteria:

Primary Endpoint:

Progression-free survival defined as the time from randomization to the time of first documented IRC-assessed disease progression per RECIST v1.1 or death due to any cause (whichever occur first).

Secondary Endpoints:

- Clinical response according to RECIST version 1.1 to evaluate ORR, DoR, and DCR.
  - ORR, defined as the proportion of patients with best overall response of complete or partial response
  - DoR, defined as the time between first documentation of a response and first evidence of progressive disease
  - DCR, defined as the proportion of patients with best response of CR or PR or SD.
- Clinical response according to irRECIST. In cases the Investigator suspects progressive disease corresponds to a pseudo-progression, such as an increase in tumor burden (including the appearance of small new lesions in new non vital areas), in the absence of significant deterioration of performance

status and laboratory values, treatment continuation is allowed until confirmation of progression with repeat imaging at least 4 weeks later or at the next regularly scheduled imaging time point.

- Survival Endpoints:
  - PFS rate at 1 and 2 years, defined as the proportion of patients with no documented progression according to RECIST version 1.1 and alive at 1 and 2 years after randomization
  - OS, defined as time from randomization to death due to any cause. Kaplan-Meier methods will be used to estimate median OS
  - OS rate at 1 and 2 years, defined as the proportion of patients alive at 1, 2 years after randomization.
- Safety and tolerability assessed throughout the study by the incidence of serious adverse events (SAE), the incidence and severity of adverse events (AEs) (coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities [MedDRA] and graded according to NCI-CTCAE version 5.0, physical examination, vital signs, electrocardiograms (ECG), and laboratory tests classified for severity using NCI-CTCAE version 5.0. Given the mechanism of action of JS001, which involves immune regulatory function, particular guidance should be given to immune-related adverse events (irAEs), Details please refer to IB.
- Serum level of (neutralizing) ADA against JS001 and trough concentration measured every 4 cycles in first year then after measured every 8 cycles until disease progression to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety and efficacy.
- Quality of Life assessed by the EORTC QLQ-C30, EORTC QLQ-H&N35 questionnaire and ECOG performance status assessments.

Exploratory endpoints:

- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers (including but not limited to PBMC, PD-L1, PD-1, tumor mutation burden and others) in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to JS001.

To evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumor volume related to the immunomodulatory activity of JS001 (i.e., pseudoprogression and tumor immune infiltration) from true disease progression.

Statistical methods:

Sample size determination

The sample size calculation is based on the primary endpoint PFS. Patients will be randomized in a 1:1 ratio. Expected median PFS time is about 7 months for standard chemotherapy. With an expected enrollment of 14 months, 280 patients (140 per arm) are needed to observe 200 PFS events at approximately 25 months after the first patient is randomized in order to detect the PFS improvement of HR = 0.67 with 80% power at a 2-sided significance level of 0.05, assuming the dropout rate is 5% over 12 months for PFS.

Analysis populations

The intent-to-treat set (ITT) will include all patients randomized. Patients will be analyzed according to the study arm to which they are randomized.

All patients receiving any amount of JS001 or placebo will be included in the safety analysis set (SS). Patients in the SS will be analyzed according to the treatment they actually received. The SS will be the primary analysis set for safety, immunogenicity, pharmacokinetics, and biomarker analyses.

The Per-Protocol Analysis Set (PPS) will include all ITT patients who do not have any major protocol violations which have significant impact on the primary outcome measures, and have valid baseline and primary output measures. Patients will be analyzed according to the study arm to which they are randomized. Major protocol violations will be defined and inclusion of subjects in the PPS population will be finalized prior to study unblinding. The PPS population will be used for some secondary/exploratory analysis as well as sensitivity analysis of the primary efficacy endpoints.

Efficacy analysis

The primary objective is to compare PFS as assessed by the IRC in ITT population (all randomized patients). The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment arm. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model will be used to assess the magnitude of the treatment difference (i.e. HR) between the treatment arms. The HR and its 95% confidence interval from the stratified Cox model will be reported. The same stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model.

Secondary analyses will be performed for PFS rates at 1 year and 2 years after randomization, and OS rates at 1 year and 2 years after randomization. The number and proportion of patients with best overall response of CR or PR or SD or progressive disease will be summarized. Objective response rate and DCR will be determined along with 95% CI. Kaplan-Meier curve will be used to estimate median DoR and OS along with 95% CI in each arm.

Safety analysis

Extent of exposure to each study drug will be summarized descriptively as the number of cycles received (number and proportion of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity, and relative dose intensity. The number (proportion) of patients requiring dose reduction, interruption, dose delay, and drug discontinuation due to AEs will be summarized for each study drug. Frequency of the above dose adjustments and discontinuation will be summarized by category. Patient data listings will be provided for all dosing records and for calculated summary statistics.

Adverse events will be coded using MedDRA version 20.0 or higher. For each study treatment, numbers of events and incidence rates will be tabulated by preferred term and system organ class. Serious adverse events, AEs leading to death, and AEs leading to withdrawal of patients will be tabulated for each arm. Commonly occurring AEs, i.e. those which occur in 5% or more of the patients in each arm, will be summarized using descriptive statistics.

All laboratory test results, physical examination results, vital signs measurements, weight, ECOG performance status, and 12-lead ECG results will be summarized for each arm using descriptive statistics at each visit for raw numbers and change from baseline.

Interim analysis

An iDMC will be set up to evaluate safety data on an ongoing basis. One interim efficacy analysis of PFS is planned when approximately 130 PFS events in the ITT population have been observed. This is expected to occur approximately 18 months after the first patient is randomized, while the exact timing of the interim analysis will depend on the actual occurrence of PFS events.

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-FU	5-fluorouracil
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BSC	Best supportive care
C-RT	Chemo-radiotherapy
CBC	Complete blood cell
CI	Confidence interval
CR	Complete response
CRO	Contract research organization
CT	Computed tomography
CTLA4	cytotoxic T-lymphocyte-associated protein 4
DCT	Disease control rate
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response

Abbreviation	Definition
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EQ-5D-5L	European Quality of Life 5-dimensons 5 Level Questionnaire
FDA	Food and Drug Administration
G-CSF	Granulocyte-colony stimulating factor
GCP	good clinical practice
GLP	good laboratory practice
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Hazard ratio
IA	Interim analysis
ICF	Informed consent form
ICH	International Council for Harmonization
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G

Abbreviation	Definition
INR	International normalized ratio
irAE	Immune-related adverse events
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reactions
irRECIST	Immune-related Response Evaluation Criteria In Solid Tumors
ITT	Intent-to-treat set
IV	intravenous
IWRS	Interactive Web response system
LOCF	Last observation carried forward
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect level
NPC	Nasopharyngeal carcinoma
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic(s)
PD-1	Programmed cell death-1

Abbreviation	Definition
PD-L1	Programmed cell death-ligand 1
PFS	Progression-free survival
PK	pharmacokinetics
PPS	Per-protocol analysis set
PR	Partial response
PT	Prothrombin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QoL	Quality of life
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SS	Safety analysis set
SD	Stable disease
SOP	Standard operating procedures
TEAE	Treatment-emergent adverse event
UC	Urothelial carcinoma
ULN	Upper limit of normal

1 Introduction

1.1 Background information

Toripalimab Injection (JS001) is a humanized IgG_{4K} (gamma 4, kappa) monoclonal antibody (mAb) specific for human programmed cell death-1 (PD-1), a co-inhibitory receptor expressed on T-cells and is being evaluated for the treatment of cancer. JS001 contains serine228 to proline substitution to minimize Fab arm exchange[1]. As with other anti-PD-1 antibodies, JS001 has a high affinity and blocks interaction between PD-1 and its ligand, programmed cell death-ligand 1 (PD-L1; B7-H1 or CD274). However, JS001 differs from other such antibodies in that the binding to PD-1 is more prolonged, as measured by the dissociation constant.

Based on the results of nonclinical pharmacology studies performed to date, JS001 binds to human PD-1, blocks the interaction between PD-1 and its ligands. JS001 inhibits the inhibitory signaling cascade that is triggered by interactions between PD-1 and its ligands. In primary cell-based assays using cells obtained from healthy donors and patients with cancer, JS001 increases T-cell proliferation and effector cytokine production following stimulation with a variety of antigens. However, in the absence of antigen or T-cell receptor engagement by a CD3 antibody, JS001 does not induce any significant cytokine release by unstimulated or pre-stimulated human T-cells in comparison with Nivolumab (Opdivo® [BMS]), Pembrolizumab (Keytruda® [Merck])or control IgG4 antibody, indicating a low risk of inducing cytokine storm.

The binding of JS001 to its target receptor, PD-1, has been characterized using enzyme-linked immunosorbent assay (ELISA)-based binding to plate-immobilized PD-1 fusion protein, flow cytometry based binding to cell surface PD-1, and Biacore based binding affinity analysis. An ELISA-based binding assay demonstrated specific interaction of JS001 with recombinant human and cynomolgus monkey PD-1 extracellular domain fusion proteins, but not with mouse or rat PD-1 fusion proteins. A Flow Cytometry-based binding assay demonstrates the binding of JS001 to human and cynomolgus monkey CD4 and CD8 T-cells. JS001 was confirmed to block interactions between PD-1 and its ligands, PD-L1 and PD-L2. Half-maximal inhibitory concentrations (IC_{50}) of JS001 were determined to be 0.8 nM for PD-L1 and 1.3 nM for PD-L2. JS001 increases T-cell proliferative response and interferon-gamma production in tetanus toxoid and Cytomegalovirus/Epstein-Barr virus (EBV)/Flu peptide recall assays. In addition, JS001 promotes nuclear factor of activated T-cells activation in a Jurkat Reporter System.

JS001 binds to PD-1 expressed on activated and memory T-cells to promote their response to antigenic stimulation. IgG4 heavy chain was selected over other heavy chain isotypes for JS001 to minimize immune effector function against the target cells.

JS001 treatment as well as Nivolumab increased CD3+/CD4+/CD8+ human T-cell counts compared with IgG4 treatment. In addition, JS001 treatment leads to complete tumor remission in MC-38 syngeneic tumor model in human PD-1 knock in mice.

Following a single intravenous (IV) infusion of JS001 for 30 minutes at doses up to 203 mg/kg to male and female cynomolgus monkeys, there was no effect on mortality, physical examinations, cageside observations, body weights, body weight changes, food consumption, or clinical pathology (clinical chemistry, hematology, coagulation, and urinalysis). The serum concentration of JS001 was quantifiable through 648 hours post-infusion in 3 animals and through 240 hours in 1 (female dosed with 1 mg/kg) animal. At study day 28, all animals had antibodies to JS001 which were not neutralizing as indicated by the long half-life. The no-observed-adverse-effect level (NOAEL) of JS001 was 203 mg/kg when administered once via IV infusion for 30 minutes to male and female cynomolgus monkeys.

In a good laboratory practice (GLP)-compliant repeat dose toxicology study, following 30 minute IV infusions every 2 weeks over 4 weeks (total of 3 doses) of JS001 at doses up to 100 mg/kg to male and female cynomolgus monkeys, there were no adverse effects on in-life parameters, ophthalmic examination findings, electrocardiogram (ECG) evaluations, clinical pathology (clinical chemistry, hematology, coagulation, and urinalysis), cytokine production, immune phenotype, gross pathology findings, absolute and relative organ weights, and histopathology findings. Although anti-drug antibodies (ADA) were observed in 2/10 monkeys in the 100 mg/kg group, 8/10 animals in the 100 mg/kg group maintained drug exposure during the course of the study. Thus, the NOAEL of JS001 in this study was 100 mg/kg when administered every 2 weeks over 4 weeks (total of 3 doses) via 30-minute IV infusion to male and female cynomolgus monkeys.

No unexpected tissue cross-reactivity was observed with JS001 in a GLP-compliant human tissue cross-reactivity study. JS001 produced plasma membrane and cytoplasmic staining of mononuclear cells in most human lymphoid tissues (including the lymph node, thymus, and tonsil, as well as gut-associated lymphoid tissue in the colon and bronchus-associated lymphoid tissue in the lung) and select non-lymphoid tissues (including in the esophagus, kidney, and cervix [cytoplasm only]). This staining was expected based on literature reports of PD-1 expression in mononuclear cell types, including T-cells, B-cells, and other myeloid cells[2,3].

Refer to the Investigator's Brochure for more detailed information about the non-clinical pharmacology, PK, and toxicology of JS001[4].

Based on analysis of all relevant preclinical pharmacology and toxicology parameters, 1 mg/kg has been selected as a starting dose, which is predicted to have partial receptor occupancy in the tumor tissue at 14 days post-dose. The selected starting dose is 1/100 of the NOAEL. In the absence of dose-limiting toxicity (DLT), the maximum dose will be 10 mg/kg; this dose level is predicted to provide sustained full receptor occupancy and represents 1/10 of the NOAEL on a mg/kg basis.

An initial dose escalation Phase I study with 3+3 design was performed in patients with advanced solid tumors (melanoma, urothelial carcinoma [UC], and renal cell carcinoma [RCC])

followed by a dose expansion phase to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, and anti-tumor activity of JS001 administered with 1 mg/kg, 3 mg/kg, or 10 mg/kg IV once every 2 weeks (Q2W) dosing schedule[5]. A total of 36 patients were enrolled. The safety and tolerability results showed that no DLT was observed and no maximum tolerated dose (MTD) was reached. The most common treatment-related adverse events (AEs) were Grade 1 or 2 in intensity and the emergence of AEs was not dose related. The clinical activity results showed that in 35 evaluable patients, an objective response rate (ORR) of 23% was reached, including complete response (CR) in 1 melanoma patient and partial response (PR) in 7 patients (3 melanoma, 2 UC, and 2 RCC). In addition, 10 patients achieved stable disease (SD) with a disease control rate (DCR) of 51%. The average time to response was 85 days. Four out of 8 patients with objective responses still had ongoing responses as of 24 May 2017, including 1 RCC patient. Pharmacokinetic (PK) analysis showed a dose-dependent linear exposure with the elimination half-life of 6 to 12 days and 6 out of 64 (9.4%) antidrug antibody (ADA) samples were positive. Using the flow cytometry method of assessing receptor occupancy, JS001 bound to the target molecule PD-1 on activated T lymphocytes with full occupancy in all patients in all cohorts after first dose of JS001. The full receptor occupancy was maintained in most patients during the study (332 day). The Phase I clinical trial data indicate that JS001 exhibits a favorable safety profile in humans. Treatment-related AEs were in line with those from approved drugs of the same class. JS001 has demonstrated promising anti-tumor activity, especially in previously under-evaluated acral and mucosal melanomas. Phase II/III clinical trials in selected indications are therefore desirable and currently ongoing.

A multi-center, open-label, Phase II registration study (CT4) was designed to evaluate safety and efficacy of JS001 in advanced melanoma patients who had failed systemic treatment. JS001 monotherapy was given at 3 mg/kg IV Q2W until disease progression or intolerable toxicity. The primary endpoint was ORR assessed by IRC pursuant to RECIST 1.1. The secondary endpoints included DOR, PFS and OS assessed by IRC. A total of 128 melanoma patients were enrolled, by March 15, 2018, 127 evaluable patients of FAS (Full analysis set) had been followed up for at least six months, One complete response，21 partial responses and 51 stable diseases were observed, representing an ORR of 17.3% and a DCR of 57.5%.In the subset of chronic UV exposure induced cutaneous melanoma subgroup, ORR and DCR was 31.03% and 65.52% respectively. There was no treatment-related death occurred in the study. The most common treatment-related adverse events were grade 1-2, including proteinuria (25%), ALT increase (25%), rash (22%), hyperglycemia (20%), amylase increase (18%), leukopenia (17%), anemia (16%), vitiligo (16%), AST increase (16%), pruritus (14%) and hypothyroidism (13%). Treatment-related adverse events of grade 3-4 occurred in 18% of patients. Therefore, at 3 mg/kg Q2W, JS001 had similar safety profile and comparable clinical efficacy with marketed PD-1 antibodies in treating metastatic melanoma. which have been filed for NDAs to the CFDA recently.

A Phase Ib/II study in patients with advanced gastric adenocarcinoma, esophageal squamous cell carcinoma, nasopharyngeal carcinoma (NPC), and head and neck squamous cell carcinoma is ongoing to evaluate the preliminary efficacy and safety of JS001 as monotherapy. The interim data showed that as of 31 Aug, 2017, 56 NPC patients (81.8% patients failed at least 2 lines of previous treatment) were enrolled into this study, 50 patients have been evaluated for clinical efficacy. Among these patients, 12 PR (partial response) and 13 SD (stable disease) were observed (ORR 24.0%, DCR 50.0%).

Refer to the Investigator's Brochure for more detailed information about the ongoing clinical trials of JS001.

1.2 Rationale

1.2.1 Rationale for the trial and selected subject population

Nasopharyngeal carcinoma (NPC), is a rare malignancy in most parts of the world with < 1 new cases/100,000 while it is endemic in a few countries[6]. In Southern China, and Southeast Asia, the estimated annual incidence of NPC is 25-50 new cases/100,000[6]. The major cause of NPC is Epstein-Barr virus (EBV) infection in conjunction with a high risk human leukocyte antigen (HLA) allotype (mainly HLA-A*11:01 and HLA-A*02:27) populations and environmental factors[7,8,9]. For advanced stage disease, overall survival (OS) at 5 years is < 10%[10].

At time of first diagnosis, according to the stage of disease, surgery, radiotherapy and chemo-radiotherapy (C-RT) are the standard treatments[11]. At time of tumor relapse, or in patients with metastatic disease at first diagnosis, standard first line chemotherapy consists of platinum based regimens. Targeting of epidermal growth factor receptor is also under exploration. Recently, the combination of gemcitabine and cisplatin was shown to be superior to that of cisplatin and 5-fluorouracil (5-FU) in terms of progression-free survival (PFS) with an increase from 5.6 months to 7.0 months and hazard ratio (HR) of 0.55, thus establishing that regimen as the standard of care[12].

Since EBV induces a high level of PD-L1 expression by cancer cells, and EBV antigens aid in immune escape, there is a good rationale to explore the role of anti-PD1 antibodies in advanced NPC[13]. Preliminary data with anti-PD-1 antibodies used alone in refractory disease have shown activity in early phase clinical studies, and randomized studies against chemotherapy are underway. The tolerability was as expected for this class of agent with Grade 3-5 treatment-related AEs including hepatitis, pneumonitis, anemia, facial pain, increase blood creatinine phosphokinase, proteinuria and sepsis, with one treatment-related death due to sepsis[14].

However, for the first line patients, a combination of chemotherapy with a PD-1 blocker can produce immunogenic cell death and yield synergistic efficacy. Such a dramatic increase in

survival is reported in other tumor types such as lung cancer (PFS HR 0.53 with the addition of pembrolizumab to chemotherapy as first line therapy).

Toripalimab Injection (JS001) is a humanized anti-PD-1 mAb. Preliminary efficacy of JS001 as monotherapy in an ongoing Phase Ib/II study in patients with advanced gastric adenocarcinoma, esophageal squamous cell carcinoma, NPC and head and neck squamous cell carcinoma has shown encouraging efficacy with 4/10 PRs in the subset of patients with NPC. In that study, JS001 monotherapy was well tolerated with no safety signal for unexpected drug-related AEs. The trial will also explore the safety and tolerability of the combination of JS001 with gemcitabine and cisplatin to support the conduct of this study. Exploratory biomarker analyses including PD-L1 level of expression as well as additional potential predictive biomarkers will be explored in this study, if applicable.

1.2.2 Rationale for dose selection

The serum trough concentration of JS001 plateaued after 3-4 consecutive doses, with the mean steady state trough concentration (C_{min}) at 20~40 μg/mL in the 3 mg/kg Q2W dose group (n = 37). In vitro binding study has showed that JS001 was able to fully saturate PD-1 receptors on T cell surface when its concentration was higher than 20 nM or 3 μg/mL. Given the penetration for antibody into tumor microenvironment, the concentration of JS001 in the peripheral blood is targeted at 25 μg/mL to ensure PD-1 receptor full occupancy on T lymphocytes in the tumor microenvironment. Results from Phase I studies showed all dose groups of 0.3, 1.0, 3.0, and 10.0 mg/kg JS001 Q2W maintained PD-1 receptor full occupancy during the entire course of treatment. Based on the PK and receptor occupancy results, 3 mg/kg Q2W was selected as the recommended Phase II dose. In the registration trial NCT03013101 in advanced melanoma (CT4), at 3 mg/kg Q2W, JS001 had similar safety profile and comparable clinical efficacy with marketed PD-1 antibodies in treating metastatic melanoma refractory to standard therapy (Section 1.1).

A fixed dose of 360 mg JS001 Q3W was also explored in two early phase trials. The PK comparison of two dosing regimens, 3 mg/kg Q2W (N = 11) and 360 mg Q3W(N = 9), showed that the steady state peak concentration of 360 mg Q3W dosing was 153% of 3 mg/kg Q2W dosing (166.53 μg/mL: 95% CI 121.0 to 212.0 vs 108.83 μg/mL: 95% CI 87.5 to 130.0); the steady state trough concentration of 360 mg Q3W dosing was 133% of 3 mg/kg Q2W dosing (47.92 μg/mL: 95% CI 31.8 to 64.0 vs 36.09 μg/mL: 95% CI 27.7 to 44.5); the estimated AUC 0-Day85 of 360 mg Q3W dosing was 138% of 3 mg/kg Q2W dosing (164993 μg/mL*hr vs 119814 μg/mL*hr). PK model extrapolation predicts the 240 mg Q3W regimen having a similar steady state trough concentration (~ 32 μg/mL) and drug exposure with the 3 mg/kg Q2W regimen. Based on the preliminary PK results and extrapolation from PK model, the results from RO and Phase II registration trial in melanoma, 240 mg Q3W is therefore selected as the recommended Phase III dose for subsequent clinical studies.

1.3 Hypothesis

The hypothesis of the study is that Toripalimab Injection (JS001) in combination with chemotherapy shows superiority compared with placebo in combination with chemotherapy in terms of PFS.

1.4 Benefit and risk assessment

Chemotherapy with gemcitabine plus cisplatin is now recognized as the standard of care for patients with recurrent or metastatic NPC. In a Phase III, multicenter, randomized, open-label trial, the median PFS was 7.0 months (95% confidence interval [CI]: 4.4-10.9 months) in patients who received gemcitabine plus cisplatin and 5.6 months (95% CI: 3.0-7.0 months) in patients who received 5-FU plus cisplatin treatment (HR 0.55 [95% CI: 0.44-0.68], p<0.0001).[12] The preliminary clinical benefit of Toripalimab Injection (JS001) as monotherapy in patients with NPC has been shown in a Phase Ib/II study and is consistent with the benefit that can be expected with PD-1 blockers in highly immunogenic tumors. Four out of 10 patients with NPC had PRs, and JS001 was tolerated well (data not published). In this study, chemotherapy will be given to all patients to ensure the standard of care is received and the additional clinical benefit of JS001 will be explored by comparing PFS after JS001 in combination with chemotherapy versus PFS after placebo in combination with chemotherapy. Benefits in terms of ORR, duration of response (DoR), DCR, and OS will also be evaluated.

The safety profile of chemotherapy with gemcitabine plus cisplatin is well established. In the Phase III, multicenter, randomized, open-label trial in patients with recurrent or metastatic NPC, the most common (> 10%) drug-related AEs for patients treated with gemcitabine plus cisplatin were leucopenia, neutropenia, anemia, thrombocytopenia, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, fatigue, weight loss, decreased appetite, nausea, and vomiting. A total of 68 (38%) and 9 (5%) patients experienced Grade 3 and Grade 4 drug-related AEs. The most common (> 10%) Grade 3-4 drug-related AEs included leucopenia, neutropenia, and thrombocytopenia. No Grade 5 drug-related AEs occurred during the study.[12]

Based on the known biology of the PD-1 pathway and its importance in immune function, the most likely class of JS001 toxicities are immune-related adverse events (irAE). The frequency and type of irAE manifestations have varied across clinical trials, depending on the treatment targets, patient populations, and the type and dosage of the drug. These symptoms led to dermatitis, enterocolitis, hepatitis, and endocrinopathies (hypophysitis, thyroiditis, adrenal insufficiency), and less often uveitis, nephritis, arthritis, and inflammatory myopathy.[15,16] Treatment with anti-PD-1 agents is commonly associated with diarrhea, although colitis, endocrinopathies, skin toxicity, fatigue and flu-like symptoms (such as fever and myalgias) are less common.[17] Eligibility criteria need to be established to exclude patients with a history of

autoimmune disease. In a Phase I study of JS001 as monotherapy in patients with advanced solid tumors (melanoma, UC, and RCC), no DLT was observed and no MTD was reached at dose levels of 1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W. The most common (> 10%) treatment-related Grade 1-2 AEs were rash, fever, leukopenia, elevated lipase, hypothyroidism, hyperthyroidism, elevated AST, hyperglycemia, anorexia, neutropenia, elevated amylase, pruritus, elevated ALT, elevated direct bilirubin, elevated total bilirubin, elevated indirect bilirubin, elevated creatine kinase, and fatigue. Six out of 36 (17%) patients were reported to have Grade 3 AEs and they included proteinuria, elevated lipase, elevated amylase, and elevated direct bilirubin. Serious adverse events were reported in 7 patients but they were all unrelated to JS001.[5] The interim analysis of the Phase Ib/II study in patients with advanced gastric adenocarcinoma, esophageal squamous cell carcinoma, NPC, and head and neck squamous cell carcinoma showed that as of Dec 30, 2017, the clinical database contained preliminary safety data from 213 patients (58 patients with GC, 59 patients with ESCC, 62 patients with NPC and 34patients with HNCC) who had received doses of JS001. Of the 213 treated patients, 95.5% experienced an adverse event regardless of attribution to JS001. Of the adverse events, 57.9% were Grade 1 or 2 in maximum severity graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI CTCAE v4.03). The most frequently observed adverse events (occurring in ≥ 10% of treated patients) included ALT increased, weight decreased, blood bilirubin increased, Platelet count decreased, nausea, abdominal pain, constipation, vomiting, diarrhea, hyponatremia, decreased appetite, asthenia, proteinuria. Treatment-related adverse events (per investigator's assessment of causality) were reported in 67.3% of patients.

2 Objectives and Endpoints

2.1 Primary objectives

The primary objective of the study is to evaluate the efficacy of Toripalimab Injection (JS001) plus chemotherapy compared with placebo plus chemotherapy, as measured by IRC-assessed PFS according to RECIST v1.1 in patients with histological/cytological confirmation of recurrent or metastatic NPC.

2.2 Secondary objectives

The secondary objectives of the study are:

- To evaluate the efficacy of Toripalimab Injection (JS001) plus chemotherapy compared with placebo plus chemotherapy, as measured by OS.
- To evaluate the efficacy of JS001 plus chemotherapy compared with placebo plus chemotherapy, as measured by investigator- and IRC-assessed ORR, DoR, and DCR according to RECIST v1.1.

- To evaluate the efficacy of JS001 plus chemotherapy compared with placebo plus chemotherapy, as measured by investigator-assessed PFS according to RECIST v1.1.
- To evaluate the IRC- and investigator-assessed PFS rate at 1 and 2 years in each treatment arm.
- To evaluate the OS rate at 1 and 2 years in each treatment arm.
- To assess disease-related symptoms and HRQoL in patients treated with JS001 plus chemotherapy compared with placebo plus chemotherapy using the EORTC QLQ-C30, EORTC QLQ-H&N35 and ECOG performance status assessments.
- To evaluate the safety and tolerability of JS001 plus chemotherapy compared with placebo plus chemotherapy.
- To evaluate the incidence and titers of ADAs against JS001 and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy.
- To evaluate the efficacy of JS001 plus chemotherapy compared with placebo plus chemotherapy, as measured by investigator- and IRC-assessed PFS, ORR, DoR and DCR according to irRECIST.

2.3 Exploratory objectives

The exploratory objectives of the study are:

- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers (including but not limited to PMBC, PD-L1, PD-1, tumor mutation burden and others) in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to Toripalimab Injection (JS001).
- To evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumor volume related to the immunomodulatory activity of JS001 (i.e., pseudoprogression and tumor immune infiltration) from true disease progression.

3 Study Design

3.1 Description of the study

This is a randomized, placebo-controlled, multi-center, double blinded, Phase III study to determine the efficacy and safety of Toripalimab Injection (JS001) in combination with gemcitabine/cisplatin compared with placebo in combination with gemcitabine/cisplatin as first-line treatment in patients with histological/cytological confirmation of recurrent or metastatic NPC. The primary endpoint is PFS in all patients. The availability of an archival or fresh tumor biopsy sample is mandatory for histological confirmation of NPC, PD-L1 expression level and

for correlative analyses (i.e., PD-L1 expression). Follow-up optional tissue and/or liquid biopsies will be collected for exploratory PD tests.

Approximately 280 patients who fulfill all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to one of the two treatment arms according to the following stratification factors:

- ECOG performance status (0 versus 1)
- Disease stage (recurrent versus metastatic)

After stratification, patients will be randomly assigned by Interactive Web Response System (IWRS) to the combination of JS001 (Arm A) or placebo (Arm B) with gemcitabine and cisplatin given every 3 weeks (Q3W) in 3-week cycles. **Day 1** (baseline) will be defined as the first day a patient receives study medication. Patients will receive JS001 (Arm A) or placebo (Arm B) on Day 1 of each 3-week cycle. In Arms A & B, patients will receive gemcitabine on Days 1 & 8 and cisplatin on Day 1 of each cycle. The chemotherapy will continue until progressive disease, excessive toxicity, noncompliance, withdrawal of consent, or a maximum of 6 cycles, whichever occurs first in the 'during chemotherapy' phase. During the 'post-chemotherapy' phase, patients randomized to Arm A or Arm B will continue treatment with JS001 or placebo as maintenance therapy Q3W until excessive toxicity or progressive disease, withdrawal of consent or Investigator's judgement or a maximum of 2 years. Patients may continue treatment with JS001 (Arm A) or placebo (Arm B) beyond radiographic progression by the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, provided they are experiencing clinical benefit, as assessed by the Investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression, as determined by the Investigator after an integrated assessment of radiographic data and clinical status. Patients will be permitted by sponsor medical monitor or designee and treating physician to continue **JS001/placebo** after RECIST v1.1 criteria for progressive disease are met if they meet all of the criteria detailed in Section 4.6.2.

Study treatment doses and regimens are described in Section 5. Tumor evaluation scans will be performed at screening (as baseline) then every 6weeks in the first 12 months then every 9 weeks thereafter until objective disease progression. The management of patients will be based solely upon the results of the tumor evaluation scans conducted by the Investigator.

The Review Committee (IRC), consisting of independent experts will review all radiologic scans and derive the PFS, ORR, DoR and DCR, according to RECIST 1.1 and irRECIST. Details will be provided in a separate charter.

To take into account the specificities of imaging after an immuno-modulating agent, both the RECIST version 1.1 and irRECIST will be used to evaluate tumor response. To date, it is considered that a 2-year period of therapy is adequate to yield the maximum effect of immunotherapeutics. Therefore, after the during chemotherapy phase, responding or stabilized

patients will be offered to continue with JS001 or placebo as maintenance therapy over a maximum of 2 years. Thereafter, patients can continue on BSC or start a new therapy as indicated in case of relapse.

This is a double blinded, one interim efficacy analysis of PFS is planned and pre-defined stopping boundary is set for two-sided p-value. The iDMC will provide the recommendation as to whether to unblind the study or not according to the data of interim analysis and the iDMC charter if the stopping boundary is crossed. If the Sponsor accepted the recommendation and unblind the study, JS001 will be provided to the patients who were randomized to arm A and still on JS001 treatment until the treatment discontinuation criteria are met according to protocol, the placebo treatment will be terminated for the patients who were randomized to arm B. After the study is unblinded, the tumor evaluation, survival follow-up, safety information, and so on information collection should be performed as required by the protocol.

The study will be conducted according to the national and international ethical standards and GCP. The protocol will be approved by the Research Ethics Committees of the participating sites.

The study design is presented in **Figure 1**.

A schedule of activities is provided in Appendix 1.

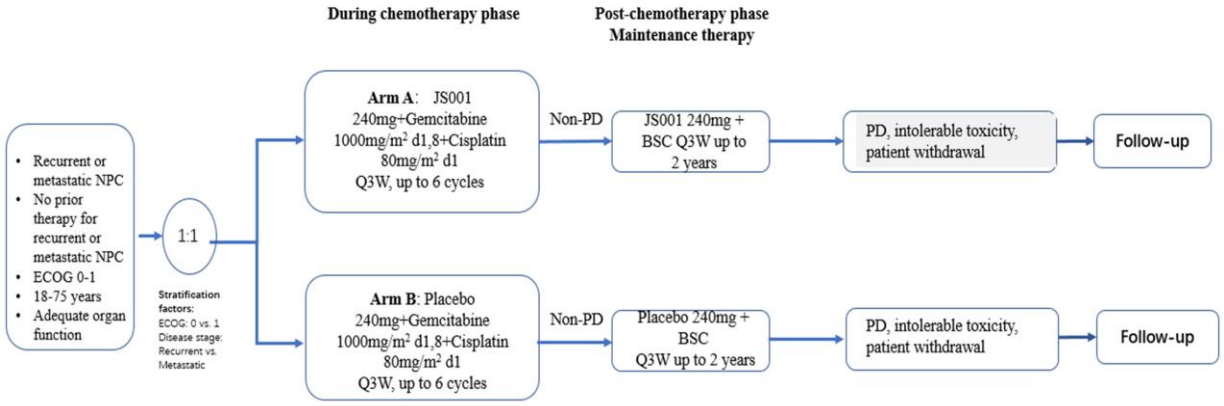

Figure 1 Study Schema

Abbreviations: BSC=best supportive care; PD=disease progression; Q3W=every 3 weeks

3.2 End of study and length of study

The final analysis of the primary efficacy endpoint will be performed when approximately 200 IRC-assessed PFS events in the intent-to-treat (ITT) population have occurred or when the last patient has been randomized, whichever occurs last. It is expected to occur at approximately 25 months after the first patient is randomized. The planned interim analysis of PFS will be treated

as the definitive efficacy analysis if the stopping boundary for the interim analysis is crossed; the interim analysis is expected to occur at approximately 18 months after the first patient is randomized (see Section 6.8 for details of the PFS interim analysis plan). If the stopping boundary is crossed and the study is unblinded, patients remaining on the experimental arm who have not progressed will be provided with toripalimab, whereas patients on the placebo arm will have placebo discontinued.

The end of study is defined as the date of the last visit of the last patient, or the date of the last data point required for efficacy analyses or safety follow-up, whichever occurs first. In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 32 months.

At the time of end of study, sponsor will continuously provide investigational product to patients who still are under treatment in accordance with local regulations.

4 Materials and Methods

4.1 Patients

Approximately 280 patients with recurrent or metastatic nasopharyngeal cancer will be enrolled in this study.

4.1.1 Inclusion criteria

A signed informed consent form must be obtained before the start of any study specific procedure. To be eligible to participate in the study, patients must meet **all** of the following Inclusion Criteria:

1. Age ≥ 18 years and ≤ 75 years.
2. An archival tumor specimen or fresh tumor biopsy sample is available.
3. Histological/cytological confirmation of NPC.
4. Primarily metastatic (stage IVB as defined by the International Union against Cancer and American Joint Committee on Cancer staging system for NPC, eighth edition) or recurrent NPC after curative treatment, which is not amenable for local regional treatment or curative treatment. No previous systemic chemotherapy was given for the recurrent or metastatic disease.
5. For the recurrent NPC after curative treatment (including radiotherapy and/or induction, concurrent or adjuvant chemotherapy), the interval between recurrence and the last dose of previous radiotherapy or chemotherapy must be more than 6 months.

6. At least 1 measurable lesion according to RECIST version 1.1.
7. Life expectancy ≥ 3 months.
8. Performance status 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) criteria (Appendix 3).
9. Adequate organ function:
    - Hematologic: leucocytes ≥ 4.0×10^9/L, Absolute Neutrophil Count ≥ 2.0×10^9/L, hemoglobin ≥ 90 g/L, and platelets ≥ 100.0×10^9/L.
    - Hepatic: bilirubin ≤ 1.5 × upper limit of normal (ULN) (patients with known Gilbert's disease who have serum bilirubin level ≤ 3 × ULN may be enrolled), AST and ALT ≤ 3 × ULN (AST/ALT ≤ 5 × ULN if liver metastases), with alkaline phosphatase ≤ 3 × ULN(ALP ≤ 5 × ULN if liver or bone metastases); albumin ≥ 3 g/dL;
    - International Normalized Ratio (INR) or Prothrombin Time (PT) or Activated Partial Thromboplastin Time (aPTT) ≤ 1.5 × ULN.
    - Renal: serum creatinine ≤ 1.5 ULN and creatinine clearance ≥ 60 mL/min according to Cockcroft-Gault formula (Appendix 8)
10. Toxicities from any prior therapy, surgery, or radiotherapy must have resolved to Grade 0 or 1 as per the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), excluding any grade alopecia.
11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures.
12. Female patients are eligible to enter and participate in the study if they are of:
    - Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who
        - Has had a hysterectomy,
        - Has had a bilateral oophorectomy (ovariectomy),
        - Has had a bilateral tubal ligation, or
        - Is post-menopausal (total cessation of menses for ≥ 1 year).
    - Childbearing potential, has a negative serum pregnancy test at screening (within 7 days of the first investigational product administration), and uses adequate contraception before study entry and throughout the study until 60 days after the last investigational product administration. Adequate contraception, when used consistently and in accordance with both the product label and the instructions of the physician, are defined as follows:
        - Any intrauterine device with a documented failure rate of less than 1% per year.

- Double barrier contraception defined as condom with spermicidal jelly, foam, suppository, or film; OR diaphragm with spermicide; OR male condom and diaphragm.

4.1.2 Exclusion criteria

Patients will be excluded from the study, if **any** of the following criteria is met:

1. History of severe hypersensitivity reactions to other mAbs or any ingredient of Toripalimab Injection (JS001).
2. Active or untreated CNS metastases (e.g., brain or leptomeningeal), as determined on CT or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments. Patients who have prior therapies for brain or leptomeningeal metastasis and has been stabilized for ≥ 2 months and has discontinued systemic steroids therapy (>10 mg/day prednisone or equivalent) > 4 weeks prior to randomization could be included.
3. Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 2 weeks prior to randomization
4. Patients with necrotic lesions have potential risk of massive hemorrhage at the discretion of investigator.
5. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures. Patients with indwelling catheters (e.g., PleurX® catheter) are allowed.
6. Uncontrolled tumor-related pain

   Patients requiring pain medication must be on a stable regimen at study entry.

   Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment.

   Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to enrollment.
7. Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium greater than the ULN)
8. Malignancies other than NPC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix,

basal or squamous cell skin cancer, localized prostate cancer treated with curative intent, ductal carcinoma in situ treated surgically with curative intent)

9. Prior therapy targeting PD-1 receptor, or its ligand PD-L1, or cytotoxic T-lymphocyte-associated protein 4 (CTLA4) receptor.
10. Use of antineoplastic traditional herbal medicine within 4 weeks before randomization.
11. Major surgical procedure other than for diagnosis of NPC within 28 days prior to randomization or anticipation of need for a major surgical procedure during the study.
12. History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain -Barrésyndrome, multiple sclerosis, vasculiti s, or glomerulonephritis (see Appendix 11 for a more comprehensive list of autoimmune diseases).

    Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study.

    Patients with controlled Type I diabetes mellitus on a stable insulin regimen are eligible for this study.
13. Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or IL-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to randomization.
14. Treatment with systemic corticosteroids (> 10 mg daily prednisone equivalents) or other systemic immunosuppressive medications (including, but not limited to, prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to randomization. Use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids is allowed.

    Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.

    Patients with history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments performed on MRI.

    The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency is allowed.
15. Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation.

16. History of idiopathic pulmonary fibrosis, drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans), idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.
17. History of hypersensitivity to gemcitabine or cisplatin or to any of the excipients.
18. Use of any live vaccines (e.g., against infectious diseases such as influenza, varicella, etc.) within 4 weeks (28 days) before randomization.
19. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result and HBV DNA detected by study site lab ≥ 1000 cps/mL or the lower limit of the local lab), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies).

    Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible only if they are negative for HBV DNA (HBV DNA detected by study site lab < 1000 cps/mL or the lower limit of the local lab).

    Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
20. Underlying medical conditions with clinical significance (such as dyspnea, pneumonitis, pancreatitis, uncontrollable diabetes, active or uncontrollable infection, drug or alcohol abuse, or psychiatric conditions), which in the Investigator's opinion can affect the administration of study drugs and protocol compliance.
21. Presence of a significant neurological or psychiatric disease, including dementia and seizures.
22. Have NCI-CTCAE ≥ Grade 2 peripheral neuropathy.
23. Female patients who are at pregnancy or lactation.
24. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater, Appendix 6), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina.

    Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

4.1.3 Other eligibility criteria consideration

To assess any potential impact on patient eligibility with regards to safety, the Investigator must refer to the IB for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the investigational product being used in this study.

Re-screening under limited conditions should be allowed after consultation with the Sponsor, e.g. when a patient narrowly misses a lab criterion and it's correctable and not due to rapidly deteriorating condition or progressive disease. Multiple attempts should not be allowed for re-screening.

4.1.4 Patient restrictions

The following restrictions may affect patient participation in this study:

- Availability to attend visits according to the protocol.
- Concomitant medication restrictions as described in Section 4.4.
- Women of child-bearing potential must use a double-barrier method of contraception during the study and for at least 60 days following the last dose of study drug and male patients must use appropriate contraception methods (total abstinence or condom with spermicide) for at least 60 days after the last dose of study drug.
- Male patients with a female partner of childbearing potential
    - Nonsterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 60 days after receipt of the final dose of Toripalimab Injection (JS001) /placebo in combination chemotherapy or 60 days after receipt of the final dose of JS001/placebo monotherapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.
    - Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (the same request with female patients).
- Strenuous exercise should be avoided up to 72 hours before planned study visits.

4.2 Method of treatment assignment and blinding

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. Toripalimab Injection (JS001) and placebo will be identical in physical appearance. The treatment each patient will receive will not be disclosed to the Investigator, study center staff, patient, Sponsor, CRO or the IRC. The treatment codes will be held by the

Clinical Supplies Department of the Sponsor. After written informed consent has been obtained and eligibility has been established, personnel at the study site will enter demographic and baseline characteristics in the IWRS. For patients eligible for enrollment, the study site will obtain the patient's randomization number and treatment assignment from the IWRS. Randomization to one of the two treatment arms will occur in a 1:1 ratio.

Permuted-block randomization will be applied to ensure a balanced treatment assignment with respect to the prespecified stratification factors as follows:

- ECOG performance status (0 versus 1)
- Disease stage (recurrent versus metastatic)

Patients should receive their first dose of study treatment on the day of randomization if possible. If this is not possible, the first dose should occur within 3 calendar days after randomization.

While ADA and trough concentration samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, ADA and trough concentration assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial. Sponsor personnel or designee responsible for performing ADA and trough concentration assays will be unblinded to patients' treatment assignments to identify appropriate ADA and trough concentration samples to be analyzed. Samples from patients assigned to the comparator arm will not be analyzed except by request (e.g., to evaluate a possible error in dosing).

The Sponsor will offer post-trial access to the study drug Toripalimab (JS001) free of charge to eligible patients that was assigned to Arm A after 2 years of treatment. For the patients who intent to receive study drug after completing the study will be unblinded. Only patients who are found to be randomized to Arm A may continue to receive Toripalimab (JS001) rechallenge (more details refer to section 4.3.4).

The process for breaking the blind will be handled through the IWRS. Investigators are strongly discouraged from requesting the blind be broken for an individual patient. If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IWRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly.

The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event). Any site that breaks the blind under inappropriate circumstances may be asked to discontinue its participation in the study.

The Sponsor and CRO must be notified immediately if a patient and/or Investigator is unblinded during the course of the study. Pertinent information regarding the circumstances of unblinding of a patient's treatment code must be documented in the patient's source documents and electronic case report forms (eCRFs).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.9) that are considered by the investigator or Sponsor to be related to study drug.

At the time of end of study, patients who still are under treatment will be unblinded. Only patients who are found to be randomized to the JS001 arm may continue to receive JS001 treatment.

Before the end of study, all the patients would be unblinded in advance if the pre-defined stopping boundary is crossed and the Sponsor accepted the recommendation of unblind the study recommended by iDMC. JS001 will be provided to the patients who were randomized to JS001 arm and still under JS001 treatment until the treatment discontinuation criteria are met according to protocol, the placebo treatment will be terminated for the patients who were randomized to placebo arm. The tumor evaluation, survival follow-up, and safety information, and so on information collection should be performed as required by the protocol.

4.3 Study treatment

4.3.1 Formulation, packaging, and handling

4.3.1.1 Toripalimab injection (JS001) /placebo

JS001 is a humanized modified IgG4κ mAb specific against human PD-1. JS001 contains the complementarity-determining regions of a murine antibody that binds to human PD-1 and human framework regions with limited back-mutations to the parental murine sequence. A serine to proline substitution was introduced at amino acid 228 to minimize Fab arm exchange. JS001 is produced by recombinant DNA technology in a Chinese Hamster Ovary mammalian cell expression system (LONZA). JS001 has a predicted molecular weight of approximately 147 kDa, and it is composed of two 452 amino acid heavy chains and two 219 amino acid light chains. JS001 contains an N-linked glycosylation site at heavy chain amino acid 302. The isoelectric point of JS001 is between 6.4 and 7.4. The JS001 drug product is a 6 mL sterile liquid form filled in a glass vial configuration (West Flurotec® stopper and aluminum crimp) to be administered IV. The JS001 drug product formulation is shown in **Table 1** and should be stored at 2-8℃.

Placebo formulation is also shown in **Table 1** and should be stored at 2-8℃.

Table 1 Toripalimab Injection (JS001) and Placebo Formulations

Test/reference drug	Manufacturer	Concentration and formulation as supplied
Toripalimab Injection (JS001)	Suzhou Union Biopharm. Co. Ltd.	Supplied as a sterile liquid containing 240 mg JS001. JS001 is formulated at a nominal concentration of 40 mg/mL in 20 mM Sodium Citrate, 2.5% (w/v) Mannitol, 50 mM NaCl, 0.02% (w/v) Polysorbate 80, pH 6.0. Each vial contains 6 mL of available volume.
Placebo	Suzhou Union Biopharm. Co. Ltd. 999 Longqiao Rd,Suzhou, Jiangsu, 215200, China	Supplied as a sterile liquid containing 20 mM Sodium Citrate, 2.5% (w/v) Mannitol, 50 mM NaCl, 0.02% (w/v) Polysorbate 80, pH 6.0. Each vial contains 6 mL of available volume.

NaCl = sodium chloride.

The JS001 drug product or placebo is aseptically filled in a 6 mL glass vial configuration (West Flurotec ® stopper and aluminum crimp) and supplied to sites in separate multi-patient cartons. Each carton contains 1 vial. White labels will be applied to cartons and vials containing JS001 or placebo. No other coding will be included.

The primary labeling on the vials contains the following information: protocol number, content and quality of JS001 or placebo, batch number, expiry date, storage instruction, and administration instructions. The content of the label will be in accordance with Good Manufacture Practice and local regulatory requirement. If applicable, label text will be translated into local languages, as required.

JS001/placebo will be supplied by the sponsor.

4.3.1.2 Gemcitabine and cisplatin

The associated products in this study include gemcitabine and cisplatin. Each drug will be used in the commercially available formulation and will be provided by the Sponsor.

For information on the formulation, packaging, and handling of gemcitabine and cisplatin, see the local prescribing information for each drug.

4.3.2 Dosage, administration, and compliance

4.3.2.1 Toripalimab injection (JS001) /placebo in combination with gemcitabine and cisplatin

Patients will receive 240 mg JS001/placebo administered by IV infusion Q3W in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. JS001/placebo will be administered in 100-mL 0.9% NaCl IV infusion bags at the dose of 240 mg as an intravenous infusion (IV) over 60 (± 15) minutes followed by a 60-minute observation period (only required in the first 2 cycles). If no clinically significant infusion reactions are observed during or after the first 2 cycles, JS001/placebo will be administrated as a 30-minute IV infusion (±10 minutes is permitted). JS001 /placebo is given first on Day 1 of each cycle.

JS001/placebo infusions will be administered per the instructions outline in **Table 2**.

Table 2 Administration of First and Subsequent Infusions of JS001/Placebo*

First Infusion	Subsequent Infusions
• No pre-medication is allowed. • Infuse JS001/placebo over 60 (± 15) minutes • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) at 60 (± 10) minutes after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If patient experienced infusion-related reaction during any previous infusion, pre-medication with antihistamines may be administered for Cycles ≥ 2 at the discretion of the treating physician. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) 60 min (± 10) after the second infusion. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion if clinically indicated or patient experienced symptoms during the previous infusion. • If no reaction occurs during the first 2 infusions, continue subsequent infusions 30 minutes (±10 minutes is permitted) without following 60-minute observation period. • If an infusion-related reaction occurred during a previous infusion, subsequent infusions should be administered over at least 2 hours and patients should be observed post-infusion. Vital signs should be obtained during and post-infusion.

* Refer to most recent version of the Investigator's Brochure and Appendix 13 concerning the management of an infusion-related reaction.

Gemcitabine and cisplatin are given according to drug label and to local standards for premedication and prophylactic medications. gemcitabine 1000 mg/m^2 over 30 minutes IV is given on Days 1 and 8, and cisplatin 80 mg/m^2 IV over 4 hours is given on Day 1, in 3-week cycles for up to 6 cycles. The formula for body surface area calculation is provided in Appendix 7.

The chemotherapy will continue until progressive disease, excessive toxicity, noncompliance, withdrawal of consent, or a maximum of 6 cycles, whichever occurs first in the 'during chemotherapy' phase. During the 'post-chemotherapy' phase, patients A will continue treatment with JS001/placebo as maintenance therapy Q3W until excessive toxicity or progressive disease, withdrawal of consent or Investigator's judgement or a maximum of 2 years.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.3.3.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration Electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.3 Investigational medicinal product accountability

The investigational medicinal products (IMP) for this study are Toripalimab Injection (JS001) and placebo. Depending on local classification, in this study, gemcitabine and cisplatin are considered a non-investigational medicinal product (NIMP). All IMPs and NIMPs required for completion of this study (JS001/placebo, gemcitabine and cisplatin) will be provided by the Sponsor.

The study site will acknowledge receipt of IMPs with use of IWRS to confirm shipment condition and content. Any damaged shipments will be replaced.

IMPs and NIMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP/NIMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP/NIMP is destroyed, and IMP/NIMP destruction must be documented on the appropriate form.

Accurate records of all IMPs and NIMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-trial access to toripalimab injection (JS001)

The Sponsor will offer post-trial access to the study drug JS001 free of charge to eligible patients that was assigned to Arm A after 2 years of treatment, as outlined below.

A patient will be eligible to receive study drug JS001 after completing the study if **all** of the following conditions are met:

- The disease progressed after JS001 discontinuation.

- At investigator's discretion, the patient will derive benefit from JS001 rechallenge.
- The patient has a life-threatening or severe medical condition and requires continued study drug JS001 treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will **not** be eligible to receive study drug JS001 after completing the study if **any** of the following conditions are met:

- The study drug JS001 is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug JS001 or data suggest that the study drug JS001 is not effective for recurrent or metastatic NPC.
- The Sponsor has reasonable safety concerns regarding the study drug JS001 as treatment for recurrent or metastatic NPC.
- Provision of study drug JS001 is not permitted under the laws and regulations of the patient's country.

4.4 Concomitant therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug to the treatment discontinuation visit (within 30 days after the last dose of study drugs or the actual day of the treatment discontinuation visit, whichever occurs first). All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF, all the concomitant medication administrated for the management of AE/SAE (refer to section 5.5.1) occurred after the treatment discontinuation visit should be recorded on the Concomitant Medications eCRF.

4.4.1 Permitted therapy

Premedication with antihistamines may be administered for any Toripalimab Injection (JS001) infusions after Cycle 1.

The following therapies should continue while patients are on study:

- Anticonvulsants: Cisplatin may lower the serum levels of anticonvulsants. Subjects receiving anticonvulsants should undergo frequent assessments of their serum levels to ensure that a therapeutic concentration is maintained.
- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level)
- Palliative radiotherapy (e.g., treatment of known bony metastases) if the lesion to be irradiated is not the only site of disease as that would render the patient not evaluable for response by tumor assessments according to RECIST v1.1, but patient will remain evaluable for progression
- Inactive influenza vaccinations during influenza season ONLY
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, as per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist as per standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists; see Appendix 12).

All medications must be recorded on the Concomitant Medications Electronic Case Report Form (eCRF).

4.4.2 Prohibited therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority –approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the anti-cancer agent (see Section 4.1.2), and during study treatment until disease progression is documented and patient has discontinued study treatment. This

includes but is not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy.

The following medications are prohibited while on study, unless otherwise noted:

- Traditional herbal medicines as their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity
- Denosumab; patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study.
- Any live, attenuated vaccine (e.g., FluMist®) within 4 weeks prior to randomization or at any time during the study
- Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, MRIs of the nasopharynx, neck, abdomen with a non-contrast CT scan of the chest must be performed.
- Prophylactic G-CSF are not allowed before the first cycle. Thereafter, they must be administered curatively and preventively according to the severity of neutropenia.

4.5 Study assessments

Flowcharts of scheduled study assessments are provided in Appendix 1.

Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

4.5.1 Informed consent forms and screening log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations and may be obtained within 28 days before initiation of study treatment.

Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients pre-screened and/or screened and to confirm eligibility or record reasons for screening failure, as applicable.

Patients who are treated with IMPs and who show apparent radiographic progression at a tumor response evaluation and have alternative anti-cancer therapies available to them must sign consent at that time to acknowledge deferring these treatment options before continuing treatment JS001/placebo, and to have a biopsy of the progressing lesion is strongly recommended.

4.5.2 Medical history and demographic data

Medical history includes clinically significant diseases, surgeries, non-NPC cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit.

NPC cancer history will include prior cancer therapies, procedures.

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

4.5.3 Physical examinations

A complete physical examination, according to local practice, should be performed at screening. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital signs

Vital signs will include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature.

4.5.5 Tumor and response evaluations

Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRIs of the nasopharynx, neck, chest and abdomen. A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Patients with active or untreated CNS metastases are not eligible for this study.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

Bone scans should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Response will be assessed by the investigator using RECIST v1.1 (see Appendix 4) and irRECIST (see Appendix 5). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

Tumor assessments will be performed every 6 weeks (± 7 days) for 12 months following Cycle 1, Day 1 and then every 9 weeks (± 7 days) thereafter, regardless of treatment delays, until disease progression per RECIST v1.1 (for patients in both treatment arms), loss of clinical benefit (for patients who continue treatment after disease progression according to RECIST v1.1) withdrawal of consent, initiation of new anti-cancer therapy, death, or study termination by the Sponsor, whichever occurs first. At the investigator's discretion, CT scans should be repeated at any time if progressive disease is suspected.

Patients who are treated with Toripalimab Injection (JS001) /placebo who continue to experience clinical benefit, despite evidence of radiographic progression, will continue tumor assessments as per the schedule listed above.

Scans will be submitted for central review to an IRC.

4.5.6 Laboratory, biomarker, and other biological samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)
- Coagulation (INR, PT, aPTT)
- Serum pregnancy test should only be conducted at screening period for women of childbearing potential, including women who have had a tubal ligation; urine pregnancy tests will be performed at each cycle during treatment. A serum pregnancy test must be performed if the urine pregnancy test is positive.

  Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy or not being postmenopausal (≥ 12 months of amenorrhea).
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood), dipstick permitted; and microscopic examination (sediment, RBCs, WBCs).
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)
- HBV serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen [anti-HBc])
- HBV DNA should be obtained prior to randomization if patient has positive serology for anti-HBc Ab.
- HCV serology (anti-HCV)
- HIV testing

  All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical trial.

  A central laboratory will coordinate the sample collection of tissue and blood samples for research-related testing at central laboratories or at the Sponsor. Instruction manuals and supply kits will be provided for all central laboratory assessments. Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:
- Epstein-Barr virus serology
- PD-L1 assays
- ADA and trough concentration assays (patients assigned to Arm A only)

  Serum samples will be assayed for the presence of ADAs to JS001 and trough concentration of JS001 with use of validated immunoassays.

- Biomarker assays in blood samples

  Blood samples will be obtained for biomarker evaluation (including but not limited to biomarkers that are related to NPC or tumor immune biology) from all eligible patients according to the schedule in Appendix 2. Samples will be processed to obtain plasma and serum for the determination of changes in blood-based biomarkers (e.g., ctDNA, cytokines). Whole blood samples may be processed to obtain peripheral blood mononuclear cells and their derivatives (e.g., RNA and DNA) and may be evaluated for immune-related, tumor type–related, and other exploratory biomarkers (e.g., alterations in gene expression or single nucleotide polymorphisms).

  Any remaining samples collected for biomarker assays, ADAs and trough concentration may be used for exploratory biomarker profiling, identification, and additional safety assessments as appropriate.

See the laboratory manual for additional details on laboratory assessments and sample handling.

4.5.7 Tumor tissue samples

A central laboratory will coordinate the sample collection of tissue samples for research-related testing at central laboratories or at the Sponsor. Instruction manuals and supply kits will be provided for all central laboratory assessments.

See the laboratory manual for additional details on tissue sample handling.

4.5.7.1 Archival or freshly collected tumor tissue samples at screening

A pre-treatment tumor tissue (archival or freshly obtained) sample should be submitted before or within 4 weeks after enrollment. This specimen must be accompanied by the associated pathology report. Although any available tumor tissue sample can be submitted, it is strongly encouraged that the sites submit representative tumor specimens in paraffin blocks (preferred) or 8 (or more) serial, freshly cut, unstained slides exploratory biomarker analysis (including, but not limited to, markers related to immune or NPC biology, such as PD-L1expression, tumor mutation burden and tumor infiltration CD8+ lymphocyte).

The preferred sample types include: resections, core needle, excisional, incisional, punch, or forceps biopsies. Tumor tissue should be of good quality based on total and viable tumor content. Tumor tissue from bone metastases that is subject to decalcification is not advisable.

4.5.7.2 Optional tumor samples at the time of radiographic progression

Patients in all treatment arms can undergo an optional tumor biopsy to obtain a tumor sample at the time of radiographic disease progression (preferably within 40 days of radiographic progression or prior to start of the next anti-cancer treatment, whichever is sooner) if they have provided consent for Optional Biopsy.

The preferred sample types include: resections, core needle, excisional, incisional, punch, or forceps biopsies. If such specimens are not available, any type of specimens including fine-needle aspiration, cell pellet specimens (e.g., from pleural effusion and lavage samples) can also be submitted.

4.5.8 Electrocardiograms and echocardiogram

A twelve-lead ECG is required at screening and as clinically indicated. ECGs should be obtained on the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine position.

An echocardiogram to assess left ventricular ejection fraction (LVEF) will be conducted at screening and then if clinically indicated thereafter until discontinuation of study drug. The patients should also be examined using the same machine and operator whenever possible.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings and echocardiogram report. Paper copies of ECG tracings and echocardiogram report will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities and echocardiogram abnormalities must be documented on the eCRF.

4.5.9 Patient-reported outcomes (PRO)

PRO data will be collected via the EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires to more fully characterize the clinical profile of Toripalimab Injection (JS001).

The questionnaires will be translated as required in the local language. To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient prior to the performance of non-PRO assessments which will relate to disease status assessment, and the administration of study treatment.

4.5.10 Timing of assessment

4.5.10.1 Screening/baseline assessment

Screening tests and evaluations will be performed within 28 days prior to Cycle 1, Day 1. Pregnancy test and key lab tests will be obtained within 7 days prior to Cycle 1, Day 1 (See Appendix 1). Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1, Day 1 may be used; such tests do not need to be repeated for screening.

See Appendix 1 for the schedule of screening assessments and Appendix 2 for the schedule of ADA, trough concentration, and biomarker sampling.

4.5.10.2 Assessments during treatment

All treatment visits must occur within ± 3 days from the scheduled date unless otherwise noted (see Appendix 1). All procedures, tests and assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted.

If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing and visits continuing on a 21-day schedule. If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

See Appendix 1 and Appendix 2 for the schedule of treatment period.

4.5.10.3 Assessment at treatment discontinuation visit

Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study treatment. The visit at which a response assessment shows progressive disease according to RECIST v1.1 or loss of clinical benefit may be used as the treatment discontinuation visit. If the study drug infusion delayed and discontinued subsequently, and the interval between last dose of study treatment and decision of treatment discontinuation probably is near or longer than 30 days, the investigator should complete Treatment Discontinuation Visit as early as they can after patients formally withdrawal from study treatment.

See the study flowcharts provided in Appendix 1 and Appendix 2 for assessments to be performed at the treatment discontinuation visit.

Patients who discontinue study treatment must be followed according to the follow-up visit schedule for progression and/or survival until death, loss to follow-up, or withdrawal of consent, which will be defined as study discontinuation.

4.5.10.4 Follow-up assessment

After the Treatment Discontinuation Visit, adverse events should be followed as outlined in Section 5.5.1.

For patients who discontinue study treatment for any reason other than progressive disease, tumor assessments should continue at the same frequency as would have been followed if the patient had remained on study treatment until disease progression, loss of clinical benefit, initiation of new anti-cancer therapy, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

See the study flowcharts provided in Appendix 1 and Appendix 2 for assessments to be performed during Follow-Up visits.

4.5.10.5 Assessment at unscheduled visits

Assessments for unscheduled visits related to a patient's underlying diseases, study treatment, or adverse events should be performed as clinically indicated and entered into Unscheduled Visit eCRFs.

4.6 Patient, Treatment, Study, and Site Discontinuation

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status
- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another non-protocol anti-cancer therapy (see Section 4.4.2)
- Pregnancy
- Radiographic disease progression per RECIST v1.1

Exception: Patients will be permitted by sponsor medical monitor or designee and treating physician to continue **Toripalimab Injection (JS001) /placebo** after RECIST v1.1 criteria for progressive disease are met if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing
- Patients must provide written consent to acknowledge deferring any standard treatment options that may exist in favor of continuing JS001/placebo treatment at the time of initial progression.

Patients who experience second progression (taking as reference the smallest sum after first progression) according to RECIST v1.1 should permanently discontinue JS001/placebo treatment.

In during chemotherapy phase, if patients experience progressive disease according to RECIST v1.1 criteria, chemotherapy must be discontinued without exception.

The primary reason for study drug discontinuation should be documented on the appropriate eCRF.

4.6.3 Study and Site Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5 Assessment of Safety

JS001 has been approved for the treatment of patients with unresectable or metastatic melanoma with disease progression on or after previous systemic treatment on the basis of a single arm trial in December 2018 in China. The indications for nasopharyngeal carcinoma are currently in clinical development. Human experience is currently limited and the entire safety profile is not known at this time. The following information is based on results from nonclinical and clinical studies and published data on similar molecules.

5.1 Safety plan

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2) and close monitoring (as indicated below and in Section 4.5). See Section 5.5 for complete details regarding safety reporting for this study.

Administration of Toripalimab Injection (JS001)/placebo will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. All adverse events and serious adverse events will be recorded during the trial and for up to 60 days after the last dose of study treatment. Investigators are instructed to report all serious adverse events considered related to study

treatment regardless of time after study. The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

5.2 Risks associated with toripalimab injection (JS001)

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions. Adverse events with potentially immune-mediated causes, including interstitial lung disease, hypothyroidism and hyperthyroidism, liver function disorder, pancreatitis and hyperglycemia, have been observed in previous clinical studies which investigated safety and efficacy of JS001 in solid tumors. For further details regarding clinical safety, see the JS001 Investigator's Brochure.

Suggested workup procedures for suspected immune-mediated AEs are provided in Section 5.3.3 and Appendix 13.

5.3 Risks associated with gemcitabine

Infusion times of gemcitabine longer than 60 minutes and more frequent than weekly dosing have been shown to increase toxicity.

Pulmonary toxicity has been reported with the use of gemcitabine. In cases of severe lung toxicity, gemcitabine therapy should be discontinued immediately and appropriate supportive care measures instituted.

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia has been reported with gemcitabine as a single agent or in combination with other cytotoxic drugs. Monitor for myelosuppression should occur prior to each cycle.

Hemolytic-uremic syndrome (HUS) and/or renal failure have been reported following one or more doses of gemcitabine. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS.

Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs.

Use caution in patients with pre-existing renal impairment or hepatic insufficiency.

For more details regarding the safety profile of gemcitabine, see the appropriate Package Insert.

5.3.1 Risk associated with cisplatin

Cisplatin is known to cause myelosuppression, ototoxicity, and nephrotoxicity. Cisplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for cisplatin-related adverse events.

For more details regarding the safety profile of cisplatin, refer to the appropriate package insert or national prescribing information as needed.

5.3.2 General plan to manage safety concerns

5.3.2.1 Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non–serious adverse events defined and graded according to NCI CTCAE v5.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Laboratory values must be reviewed prior to each infusion.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Appendix 1 and Appendix 2 for the list and timing of study assessments).

During the study, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

All serious adverse events will be reported in an expedited fashion (see Section 5.4.2). In addition, the iDMC and Medical Monitor will review and evaluate observed adverse events on a regular basis.

Patients will be followed for safety for 60 days following their last dose of study drug.

Patients who have an ongoing study treatment–related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

5.3.3 Toripalimab injection (JS001) /placebo dosage modification and management of specific adverse events

5.3.3.1 Dose modification

There will be no dose reduction for JS001/placebo in this study. Patients may temporarily suspend study treatment for up to 56 days beyond the last dose if they experience an adverse event that requires a dose to be held. If because of adverse events JS001/placebo is held for up to

56 days beyond the last dose, then the patient will be discontinued from treatment and will be followed for safety and efficacy as specified in Section 5.4.1.

If a patient must be tapered off steroids used to treat adverse events, JS001/placebo may be held for additional time beyond 56 days (but not more than 12 weeks) from the last dose until steroids are discontinued or reduced to ≤ 10 mg/day of prednisone or equivalent dose.

In during chemotherapy phase, for patients who suspend JS001/placebo, if the adverse event was clearly related to JS001/placebo alone, chemotherapy could continue after consulting sponsor Medical Monitor, if fulfill appropriate organ function. If the chemotherapy should be suspended due to the chemotherapy-related adverse events based on investigators' judgement, the

JS001/Placebo administration may be adjusted or not be adjusted accordingly. JS001/placebo may be continued if the adverse event was clearly related to chemotherapy alone. Overlapping toxicities that may be due to either chemotherapy or JS001/placebo (e.g., pulmonary, renal, or hepatic toxicity) should result in temporary discontinuation of both chemotherapy and JS001/placebo.

5.3.3.2 Management of toripalimab injection (JS001)/placebo specific adverse events

Toxicities associated or possibly associated with JS001/placebo treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of JS001/placebo may not have an immediate therapeutic effect and, in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF-α inhibitors.

The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of JS001/placebo. Adverse events that require temporary discontinuation of JS001/placebo must resolve to Grade 0-1 and the subject must be on ≤ 10 mg/d of prednisone or equivalent dose prior to resumption of dosing. JS001/placebo should be permanently discontinued in patients with life-threatening immune-mediated adverse events.

The most common irAEs are: fatigue, pruritus, diarrhea, decreased appetite, rash, pyrexia, cough, dyspnea, musculoskeletal pain, constipation, and nausea.

Refer to most recent version of Investigator Brochure or Appendix 13 concerning the irAEs manifestations and management[4].

5.3.4 Gemcitabine and cisplatin dose modification and management of specific adverse events

At the start of each cycle, the ANC must be ≥ 1.5 × 10^9/L and the platelet count must be ≥ 100.0×10^9/L. Treatment should be delayed for up to 42 days to allow sufficient time for recovery. Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle. Additionally, manufacturer's instructions as well as local hospital or clinical practice will also be followed.

Please note that chemotherapy dose modifications are permanent; once the dose of any agent has been reduced it will remain reduced or be further reduced in subsequent cycles. No more than 2 dose reductions are allowed.

5.3.4.1 Gemcitabine dose modification and management of specific adverse events

5.3.4.1.1 Hematologic toxicity

Dose adjustments for hematologic toxicity may be required for gemcitabine. The gemcitabine doses may be either administered at full dose (in the absence of toxicity) or at a reduced dose, as described in **Table 3** and **Table 4**. Patient receiving gemcitabine should be monitored prior to each dose with a CBC, including differential and platelet counts. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in **Table 3** and **Table 4** . Administration of D8 gemcitabine due to hematological toxicity, it can be delayed up to D15 to allow recovery, otherwise this dose should be omitted.

Table 3 Dose Modification Guidelines for Hematological Toxicities on Day 1 of Gemcitabine

Toxicity a	Gemcitabine Dose
ANC < 0.5 × 10^9/L and platelets ≥ 50.0 × 10^9/L	75% of previous dose
Platelets < 50.0 × 10^9/L, regardless of ANC	75% of previous dose
Platelets < 50.0 × 10^9/L with Grade ≥ 2 bleeding, regardless of ANC	50% of previous dose
ANC < 1.0 × 10^9/L plus fever of ≥ 38.5℃	75% of previous dose

a Nadir prior cycle.

Table 4 Dose Modification Guidelines for Hematological Toxicities on Day 8 of Gemcitabine

Absolute Neutrophil Count ($\times 10^9$/L)		Platelet Count ($\times 10^9$/L)	Gemcitabine % of previous dose (Day 1 of the cycle)
≥ 1.0	and	≥ 100.0	100%
≥ 0.5, and < 1.0	or	≥ 50.0, and < 100.0	75%
< 0.5	or	< 50.0	Hold

5.3.4.1.2 Dose modifications guidelines of non-hematological toxicity

In general, for severe (Grade 3 or 4) non-hematological toxicity, including nausea/vomiting, therapy with gemcitabine should be held or dose reduced by 50% depending on the judgment of the investigator, detailed dose modifications refer to **Table 5** Gemcitabine Dose Modification Guidelines for Non-Hematological Toxicities or local standards.

Permanently discontinue gemcitabine for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary-leak syndrome
- Posterior reversible encephalopathy syndrome

Table 5 summarizes dose modifications guidelines for non-hematologic toxicities based on grade and severity.

Table 5 Gemcitabine Dose Modification Guidelines for Non-Hematological Toxicities

	Grade 2	Grade 3	Grade 4
First appearance	Interrupt treatment until resolved to Grade 0–1 then continue at same dose with prophylaxis where possible	Interrupt treatment until resolved to Grade 0–1, then continue at 75 % of original dose with prophylaxis where possible	Discontinue treatment unless investigator considers it to be in the best interest of the patient to continue at 50% of original dose, once toxicity has resolved to Grade 0–1 (after approval by the Sponsor)
Second appearance of same toxicity	Interrupt treatment until resolved to Grade 0–1, then continue at 75% of original dose	Interrupt treatment until resolved to Grade 0–1, then continue at 50 % of original dose	

Third appearance of same toxicity	Interrupt treatment until resolved to Grade 0–1, then continue at 50 % of original dose	Discontinue treatment permanently
Fourth appearance of same toxicity	Discontinue treatment permanently	

5.3.4.2 Cisplatin dose modification and management of specific adverse events

Treatment with cisplatin should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions or immediately if a Grade 3 or 4 neurotoxicity is observed.

5.3.4.2.1 Hematologic toxicity

The cisplatin doses may be either administered at full dose (in the absence of toxicity) or at a reduced dose, as described in **Table 6**.

Table 6 Cisplatin Dose Modification for Hematologic Toxicities

Toxicity [a]	Cisplatin Dose
ANC < 0.5×10^9/Land platelets ≥ 50.0×10^9/L	75% of previous dose
Platelets < 50.0×10^9/L, regardless of ANC	75% of previous dose
Platelets < 50.0×10^9/L with Grade ≥ 2 bleeding, regardless of ANC	50% of previous dose
ANC < 1.0×10^9/L plus fever of ≥ 38.5℃	75% of previous dose

[a] Nadir prior cycle.

5.3.4.2.2 Non-hematologic toxicity

If a patient develops a Grade ≥ 3 non-hematologic toxicity (excluding alopecia, which does not warrant treatment discontinuation, and neurotoxicity), cisplatin should be withheld until resolution to less than the patient's pre-treatment value. Treatment should be resumed according to the guidelines in Table 7.

Table 7 Cisplatin Dose Modification for Non-Hematologic Toxicities (Excluding Neurotoxicity)

Toxicity	Cisplatin Dose

Any Grade 3 or 4 toxicity	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of grade) or Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication	75% of previous dose

5.3.4.2.2.1 Nephrotoxicity

Impairment of renal function has been reported with cisplatin as single agent or in combination with other cytotoxic agents. CrCl must be ≥ 60 mL/min prior to the start of any cycle. If there is a drop in CrCl between cycles, but the CrCl is still ≥ 60 mL/min at time of next cycle, the treating physician should use his/her clinical judgment regarding continuing cisplatin, dose reduction, or delaying the cycle. If a patient's CrCl value has not returned to ≥ 60 mL/min within 42 days following last cycle D1 chemotherapy administration, the patient must be discontinued from chemotherapy.

5.3.4.2.2.2 Ototoxicity

Ototoxicity has been observed with cisplatin as single agent or in combination with other cytotoxic agents. If the patient develops ototoxicity, subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits (http://www.drugs.com/pro/platinol.html).

5.3.4.2.2.3 Neurotoxicity

In the event of neurotoxicity, the recommended dose adjustment for cisplatin is documented in **Table 8**. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed.

Table 8 Cisplatin Dose Modification for Associated Neurotoxicity

Toxicity	Cisplatin Dose
Grade 0–1 neurotoxicity	100% of previous dose
Grade 2 neurotoxicity	50% of previous dose
Grade 3 or 4 neurotoxicity	Permanent discontinuation

5.4 Safety parameters and definitions

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events, performing protocol-specified safety laboratory assessments, measuring

protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.6.

5.4.1 Adverse events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered 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 5.5.5.9.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.4.2 Serious adverse events (immediately reportable to the sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.5.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.

- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.5.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.6.1 for reporting instructions).

5.4.3 Adverse events of special interest (immediately reportable to the sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), no need to report to HA. Adverse events of special interest for this study include the following:

- Suspected immune-related myocarditis: an increase in myocardial enzymes associated with changes in the electrocardiogram or clinical symptoms.
- Abnormal liver function which meet the criteria of Hy's law: elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia.

5.5 Methods and timing for capturing and assessing safety parameters

The investigator is responsible for ensuring that all adverse events (see Section 5.4.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.6 to 5.8.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.4.2 for seriousness criteria), severity (see Section 5.5.3), and causality (see Section 5.5.4).

5.5.1 Adverse event reporting period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.6.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 60 days after the last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.8).

5.5.2 Eliciting adverse event information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

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

"Have you had any new or changed health problems since you were last here?"

5.5.3 Assessment of severity of adverse events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. **Table 9** will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 9 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.6.2 for reporting instructions), per the definition of serious adverse event in Section 5.4.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.6.2 for reporting instructions), per the definition of serious adverse event in Section 5.4.2.

5.5.4 Assessment of causality of adverse events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.5.5 Procedures for recording adverse events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

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

5.5.5.1 Infusion-related reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event module. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction module. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event module, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction module.

5.5.5.2 Diagnosis versus signs and symptoms

For adverse events other than infusion-related reactions (see Section 5.5.5.1), diagnoses (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms. For example, if a patient has pain in the leg that is eventually diagnosed as being a symptom of deep vein thrombosis, then only deep vein thrombosis should be entered as an adverse event. For example, if a patient is hospitalized with shortness of breath, and pulmonary embolism, pneumonia or pneumonitis are differential diagnoses, report the appropriate adverse event term following confirmation of the diagnosis. Prior to obtaining the confirmed diagnosis, it is sufficient to report the symptoms. Once the diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by the adverse event(s) representing the diagnosis.

5.5.5.3 Adverse events that are secondary to other events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious

secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.5.5.4 Persistent or recurrent adverse events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme intensity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.6.1 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.5.5.5 Abnormal laboratory values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.5.5.4 for details on recording persistent adverse events).

5.5.5.6 Abnormal vital sign values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g. high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.5.5.4 for details on recording persistent adverse events).

5.5.5.7 Abnormal liver function tests

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, regardless of causality (including cholestasis, or other causes of hyperbilirubinemia) investigators must report as an adverse event the occurrence of either of the following:

Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin)

Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.5.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), as a serious adverse event.

5.5.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.5.1) that are attributed by the investigator solely to progression of NPC should be recorded as "**disease progression**" on the Adverse Event eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor except for those that occur due to PD after the AE reporting period, will be reported in the survival follow-up page (see Section 5.6.1).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on

the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only 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 after 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 eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

During survival follow-up, deaths attributed to progression of NPC should be recorded only on the Survival eCRF.

5.5.5.9 Preexisting medical conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.5.5.10 Worsening of nasopharyngeal cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1 criteria. In rare cases, the determination of clinical progression will be on the basis of symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is caused by disease progression, it should be reported as an adverse event.

5.5.5.11 Hospitalization or prolonged hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.4.2), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for respite care

- Planned hospitalization required by the protocol (e.g., for study drug administration or to perform an efficacy measurement for the study)
- A hospitalization that was planned prior to the study or elective surgery not caused by an adverse event
- Hospitalization caused solely by progression of the underlying cancer

5.5.5.12 Adverse events associated with an overdose or error in drug administration

Study drug overdose is the accidental or intentional use of the study drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment itself is not an adverse event, unless it results in untoward medical effects.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded in the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.6.1).

5.5.5.13 Patient-reported outcome data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.6 Immediate reporting requirements from investigator to sponsor

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.6.1 for further details)
- Pregnancies (see Section 5.6.2 for further details)

- Adverse events of special interest

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.6.1 Reporting requirements for serious adverse events

5.6.1.1 Events that occur prior to study drug initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.6.1.2 Events that occur after study drug initiation

After initiation of study drug, serious adverse events will be reported until 60 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Junshi Safety Risk Management designee.

In the event that the EDC system is unavailable, the Serious Adverse Event Reporting Form provided to investigators should be completed and submitted to Junshi designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.8.

5.6.2 Reporting requirements for pregnancies

5.6.2.1 Pregnancies in female patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 60 days after the last dose of study drug. A Pregnancy Report Form should be completed by the investigator and submitted to Junshi Safety Risk Management designee immediately (i.e., no more than 24 hours after learning of the pregnancy). Pregnancies should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until the conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.6.2.2 Pregnancies in female partners of male patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 60 days after the last dose of study drug. A Pregnancy Report Form should be completed by the investigator and submitted to Junshi Safety Risk Management designee immediately (i.e., no more than 24 hours after learning of the pregnancy). Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report Form with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.6.2.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.6.2).

5.6.2.4 Congenital anomalies/birth defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.6.2).

5.7 Follow-up of patients after adverse events

5.7.1 Investigator follow-up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.7.2 Sponsor follow-up

For serious adverse events, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.8 Post-study adverse events

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 60 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment. All deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-up eCRF.

The investigator should report these events directly to Junshi or its designee, either by faxing or by scanning and emailing the Serious Adverse Event Reporting Form using the fax number or email address provided to investigators.

5.9 Expedited reporting to health authorities, investigators, institutional review boards, and ethics committees

The Sponsor will promptly evaluate all serious adverse events against cumulative product experience to identify and expeditiously communicate the suspected adverse drug reaction that are both serious and unexpected, or possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on local regulations.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the JS001 Investigator's Brochure as a reference.

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

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An iDMC will monitor safety data during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6 Statistical Considerations and Analysis Plan

This is a randomized, placebo-controlled, multi-center, double blinded, Phase III study to evaluate the efficacy and safety of Toripalimab Injection (JS001) in combination with gemcitabine/cisplatin compared with placebo in combination with gemcitabine/cisplatin as first-line treatment in patients with histological/cytological confirmation of recurrent or metastatic NPC.

Primary and secondary analyses (PFS, OS) will be performed on all randomized patients (i.e., ITT) irrespective of whether the assigned treatment was actually received. ORR and DCR analyses will be performed on all randomized patients who have measurable disease at baseline. DOR analyses will be performed on the subset of patients who achieve an objective response. For all efficacy analyses, patients will be grouped according to the treatment assigned at randomization.

The Per-Protocol Analysis Set (PPS) will include all ITT patients who do not have any major protocol violations, which have significant impact on the primary outcome measures, and have valid baseline and primary output measures. Patients will be analyzed according to the study arm to which they are randomized. Major protocol violations will be defined and inclusion of subjects in the PPS population will be finalized prior to study unblinding. The PPS population will be used for some secondary/exploratory analysis as well as sensitivity analysis of the primary efficacy endpoints.

The safety population will include all randomized patients who received any amount of study drug. Patients who are randomized into the study but did not receive any amount of study drug will not be included in the safety population.

6.1 Determination of Sample Size

The sample size calculation is based on the primary endpoint PFS. Patients will be randomized in a 1:1 ratio. A total of 280 patients (140 per arm) are needed to observe 200 PFS events at approximately 25 months after the first patient is randomized in order to detect the PFS improvement of HR = 0.67 with 80% power at a 2-sided significance level of 0.05; The calculation of the sample size is based on the following assumptions:

- PFS is exponentially distributed.
- The median PFS is 7 months for the standard chemotherapy.
- The interim and final analyses of PFS use the Lan DeMets alpha spending function to approximate the O'Brien Fleming boundary.
- The recruitment of 280 patients will take place over 14 months.
- The dropout rate is 5% over 12 months for PFS.

6.2 Summaries of conduct of study

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 Summaries of treatment group comparability

Demographic and baseline characteristic, such as age, sex, race/ethnicity, baseline disease characteristics, ECOG performance status, EBV virus copy number and PD-L1 expression, will be summarized by treatment arm. Baseline measurements are the last available data obtained prior to the first dose of study drug.

Descriptive statistics (mean, median, SD, and range) will be presented for continuous data and frequencies and percentages will be presented for categorical data.

6.4 Efficacy analyses

6.4.1 Primary efficacy endpoint

The primary efficacy endpoint is PFS, defined as the time from randomization to the occurrence of disease progression, as determined by IRC from tumor assessments, per RECIST v1.1, or death from any cause, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization. For patients who have two consecutive missing tumor assessments, PFS will be censored at the time of the last available tumor assessment before the missing assessments. Due to COVID-19 pandemic, for patients who have two consecutive missing tumor assessments due to COVID-19 pandemic's impact, if a subsequent tumor assessment becomes available and does not show disease progression, the tumor assessment will be used in the PFS analysis and if the subsequent tumor assessment is disease progression, PFS will still be censored at the time of the last available tumor assessment before the missing assessments.

The hypothesis test for PFS will be conducted at a two-sided alpha level of 0.05. The null and alternative hypotheses can be phrased in terms of the PFS survival functions $S_A(t)$ and $S_B(t)$ for Arm A and Arm B, respectively:

$$H_0: S_A(t) = S_B(t) \text{ versus } H_1: S_A(t) \neq S_B(t)$$

The two-sided log-rank test, stratified by ECOG performance status (0 vs. 1), and disease stage (recurrent vs. metastatic), as recorded in the IWRS, will be used as the primary analysis to compare PFS between the two treatment arms. The hazard ratio (HR) for disease progression or death will be estimated with the use of a stratified Cox proportional hazards model. The 95% CI for the HR will be provided. Results from an unstratified analysis will also be provided.
The Kaplan-Meier methodology will be applied to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be developed. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm.

6.4.2 Secondary efficacy endpoints

6.4.2.1 Overall survival

The OS is defined as the time from randomization to death from any cause. Data from patients who are alive at the time of the analysis will be censored as of the last date they are known to be alive. The methods outlined for PFS will be used for the OS analysis.

6.4.2.2 Objective response rate

An objective response is defined as either a confirmed CR or a PR, as determined by the investigator and IRC using RECIST v1.1. Patients not meeting these criteria, including patients without any post baseline tumor assessment, will be considered non responders.

ORR is defined as the proportion of patients who had an objective response. The analysis population for ORR will be all randomized patients with measurable disease at baseline. An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two treatment arms will be determined using the normal approximation to the binomial distribution.

6.4.2.3 Disease control rate

DCR is defined as the rate of patients with CR or PR as best response or stable disease maintained for 6 weeks, as determined by the investigator and IRC per RECIST v1.1. The methods outlined for ORR will be used for the DCR analysis.

6.4.2.4 Duration of response

DOR will be assessed in patients who have an objective response as determined by the investigator and IRC using RECIST v1.1. DOR is defined as the time interval from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease or death is documented, whichever occurs first. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments are performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day. The methods detailed for PFS will be used for the DOR analysis.

6.4.2.5 Investigator-assessed PFS

PFS assessed by investigators per RECIST v1.1 be analyzed in the same way as done for the IRC-assessed PFS.

6.4.2.6 Survival rates of PFS and OS

The OS and investigator- and IRC-assessed PFS rates at 1 and 2 years after randomization will be estimated with the use of the Kaplan Meier methodology for each treatment arm, along with 95% CI's that are calculated with use of the standard error derived from Greenwood's formula. The 95% CI for the difference in the OS rate between the two treatment arms will be estimated with use of the normal approximation method.

6.4.2.7 Progression-free survival, objective response rate, disease control rate and duration of response per immune-related RECIST

Analyses using irRECIST for PFS, ORR, DCR and DOR as determined by the investigator and IRC will be conducted. The applicable methods outlined for PFS and ORR will be used for these analyses.

6.4.2.8 Patient-reported outcomes

Summary statistics (mean, SD, median, and range) of absolute scores and mean changes from the baseline will be calculated for all disease and/or treatment related symptom items and subscales of the EORTC QLQ-C30 and QLQ-H&N35 at each assessment timepoint for each arm during the administration of the treatment and the survival follow up period. The mean (and 95% CI) and median of the absolute scores and the changes from the baseline will be reported for interval and continuous variables. Previously-published minimally-important differences will be used to identify meaningful change from the baseline within each treatment group on the disease and/or treatment related symptoms scales[19]).

The EORTC QLQ-C30 and QLQ-H&N35 data will be scored according to the EORTC scoring manual. In the event of incomplete data, if the scale has more than 50% of the constituent items completed, a pro-rated score will be computed that is consistent with the scoring manual and the validation papers of the measure. For subscales with less than 50% of the items completed, the subscale will be considered missing. PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm.

6.4.3 Exploratory efficacy endpoints

6.4.3.1 Subgroup analyses

To assess the consistency of the study results in subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline prognostic characteristics (e.g., ECOG performance status, disease stage, EBV virus copy number, and PD-1 expression status), the IRC-assessed PFS in these subgroups will be examined. Summaries of PFS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median PFS, will be produced separately for each level of the categorical variables for the comparisons between treatment arms.

6.5 Safety analyses

Safety analyses will be performed on the safety population (see Section 6). Summaries will be presented for the safety-evaluable population by treatment arm.

Study drug exposure, including treatment duration, number of doses, and dose intensity, will be summarized for each treatment arm using descriptive statistics.

Verbatim description of adverse events will be mapped to MedDRA thesaurus terms and graded according to NCI CTCAE v5.0. All adverse events occurring during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade 3, 4, and 5), and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. The proportion of patients experiencing at least one adverse event will be reported by toxicity term and treatment arm.

Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment arm.

Laboratory data with values outside the normal ranges will be identified. In addition, selected laboratory data will be summarized by treatment arm.

Serum levels and incidence of ADA against JS001 will be summarized to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy.

6.6 Immunogenicity analyses

The incidence and titers of Anti-JS001 antibodies will be summarized descriptively to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy.

6.7 Biomarker analyses

Whole blood biomarker samples will be separated by density gradient centrifugation to acquire Peripheral Blood Mononuclear Cell (PBMC) and plasma. PBMC will be stored in liquid nitrogen and plasma will be stored at -80°C until further analysis.

Plasma or serum samples will be analyzed for EBV DNA copy number, proinflammatory cytokines, immune-checkpoint related soluble proteins, etc., upon Toripalimab Injection (JS001) treatment to explore the prognosis and potential relationship with efficacy.

Peripheral Blood Mononuclear Cell (PBMC) will be analyzed by flow cytometry for lymphocyte subgroup analysis, expression and modulation of PD-1 and other co-signaling receptors upon JS001 treatment to explore potential relationship with efficacy.

Tumor biopsy samples prior to treatment and at the time of apparent disease progression will be collected and evaluated by immune-histochemistry (IHC) staining to explore PD-L1 expression and presence of tumor infiltration CD8+ lymphocyte (TIL). For the patients enrolled in the sites of Mainland China, the pathological classification will be uniformly and clearly classified according to the World Health Organization Classification in 2017. When available, whole exon sequencing will be performed on tumor tissues to evaluate tumor mutation burden (TMB). PD-

L1 expression level and percentage, presence of CD8+ lymphocyte and TMB within tumor tissues will be analyzed for potential relationship with efficacy.

6.8 Interim analysis

An iDMC will be set up to evaluate safety data on an ongoing basis, as well as the efficacy data for the planned interim efficacy analysis. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an independent party. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. A detailed plan will be included in the iDMC Charter.

One interim efficacy analysis of PFS is planned when approximately 130 PFS events in the ITT population have been observed. This is expected to occur approximately 18 months after the first patient is randomized, while the exact timing of the interim analysis will depend on the actual occurrence of PFS events.

The final analysis of PFS will be conducted when approximately 200 PFS events in the ITT population have been observed. This is expected to occur approximately 25 months after the first patient is randomized, while the exact timing of the final analysis will depend on the actual occurrence of PFS events.

To control the type I error for PFS analyses at a two-sided significance level of 0.05, the stopping boundaries for PFS interim and final analyses have been computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundary[20] as shown in Table 10.

Table 10 Timing and Stopping Boundary of PFS Analyses

Type of Analysis	Timing Since FSI (month)	Planned Information Fraction (Event #)	Stopping Boundary (Two-Sided p-Value)
PFS interim analysis	18	65% (130)	0.011
PFS final analysis	25	100% (200)	0.047

FSI = First subject in; PFS = progression-free survival; HR = hazard ratio.

7 Data Collection and Management

7.1 Data quality assurance

A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of

discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor or CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and CRO's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

7.2 Electronic case report forms

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 Source data documentation

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

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

7.4 Use of computerized systems

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 Retention of records

Records and documents pertaining to the conduct of this study and the distribution of IMP and NIMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8 Ethical Considerations

8.1 Compliance with laws and regulations

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 Informed consent

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Form will contain a separate section that addresses the collection of optional samples and the disposition of remaining mandatory samples (plasma, serum, whole blood, and tissue) for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent and/or specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow the collection of optional samples for exploratory research and to inform subjects about the disposition of the remaining specimens. Patients who decline to participate will not provide a separate signature.

The Informed Consent Form will also contain the following additional signature pages:

- A signature page for patients receiving Toripalimab Injection (JS001) /placebo who choose, if approved by the treating physician and sponsor medical monitor or designee, to continue treatment beyond initial radiographic disease progression and meet the criteria specified in Section 4.6.2. This separate consent is to be signed after initial radiographic disease progression has occurred and patients have discussed other available treatment options and the potential risks of continuing treatment.

An optional Informed Consent Form will also be provided and contain a signature page for patients that consent to an optional biopsy at the time of radiographic disease progression. See Section 4.5.7.2.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 Institutional review board or ethics committee

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements of local regulations for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 Confidentiality

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 Financial Disclosure

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9 Study Documentation, Monitoring, and Administration

9.1 Study documentation

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 Protocol deviations

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 Site inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 Administrative structure

This study will be sponsored and managed by Shanghai Junshi Biosciences Co., Ltd. Approximately 40 sites in China mainland, Taiwan, Singapore, will participate in the study and approximately 280 patients will be randomized.

Randomization will occur through an IWRS. Central facilities will be used for study assessments throughout the study (e.g., specified laboratory tests). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 Publication of data and protection of trade secrets

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 Protocol amendments

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10 Independent data monitoring committee

An independent data monitoring committee (iDMC) will be assembled to evaluate safety data for this study. The iDMC will consist of at least 2 clinicians and 1 biostatistician with expertise in oncology trials. The safety of the subjects will be determined by risk/benefit assessment at periodic data review meetings until the final PFS analysis. The iDMC will also review the efficacy data for the planned interim analysis. Following the data review, the iDMC will provide a recommendation as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped. The final decision will rest with the Sponsor. A separate iDMC Charter document will specify the procedures governing the conduct of the iDMC.

11 References

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12 Appendix

12.1 Appendix 1 Schedule of Activities

	Screening [a]		All treatment cycles									Treatment Discontinuation [c]	Survival Follow-Up [d]
			During chemotherapy						Post chemotherapy		Unplanned Visit [b]		
Day (Window)	–28 to –1	–7 to –1	C1D1	C1D8	C2D1 (± 3)	C2D8	C3-C6D1 (± 3)	C3-C6D8	C7D1 (± 3)	C8D1 to PD or intolerable toxicity (± 3)	NA		
Informed consent	×[e]												
Demographic data	×												
Medical history and baseline conditions	×												
Patient-reported outcomes [f]			×		×		×		×	×			
Vital signs[g]		×	×	×	×	×	×	×	×	×	×	×	
Weight		×			×		×					×	
ECOG		×	×	×	×	×	×	×	×	×	×	×	
Height		×											
ECG[h]	×		As clinically indicated										

	Screening [a]		All treatment cycles									Treatment Discontinuation [c]	Survival Follow-Up [d]
			During chemotherapy						Post chemotherapy		Unplanned Visit [b]		
Day (Window)	–28 to –1	–7 to –1	C1D1	C1D8	C2D1 (± 3)	C2D8	C3-C6D1 (± 3)	C3-C6D8	C7D1 (± 3)	C8D1 to PD or intolerable toxicity (± 3)	NA		
Echocardiogram[h]	×	As clinically indicated											
Complete physical examination [i]	×												
Limited physical examination [j]			×		×		×		×	×		×	
Hematology [k]		×		×	×	×	×	×	×	×		×	
Coagulation test (INR, PT, aPTT)		×		As clinically indicated									
Chemistry [l]		×		×[m]	×	×[m]	×	×[m]	×	×		×	
Pregnancy test [n]		×			×		×		×	×		×	
TSH, free T3, free T4[o]	×				×		×		×	×		×	
Urinalysis [p]		×			×		×		×	×		×	
HIV, HBV, HCV serology [q]	×												

	Screening [a]		All treatment cycles									Treatment Discontinuation [c]	Survival Follow-Up [d]
			During chemotherapy						Post chemotherapy		Unplanned Visit [b]		
Day (Window)	–28 to –1	–7 to –1	C1D1	C1D8	C2D1 (± 3)	C2D8	C3-C6D1 (± 3)	C3-C6D8	C7D1 (± 3)	C8D1 to PD or intolerable toxicity (± 3)	NA		
EBV serology [r]			× [r]				× [r]		×[r]	× [r]			
Study drug administration			×	×	×	×	×	×	×	×			
Tumor response assessment	×[s]						×[t]		×[t]				
Serum sample for ADAs and trough concentration [u]			×				×		×			×	
Blood sample for biomarkers [v]			×				×		×				
Concomitant medications [w]		×	×	×	×	×	×	×	×	×	×	×	
Adverse events [x]	×		×	×	×	×	×	×	×	×	×	×	×

ADA = anti-drug antibody; eCRF = electronic Case Report Form; NA = not applicable.

Notes: All assessments should be performed within 28 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

a. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

b. Visit not specified by the protocol. Assessments should be performed as clinically indicated.

c. Patients who complete the treatment period will return to the clinic for a treatment completion visit within 30 days after the last dose of study drugs. Patients who discontinue study drug prematurely will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study drug; If the study drug infusion delayed and discontinued subsequently, and the interval between last dose of study treatment and decision of treatment discontinuation probably is near or longer than 30 days, the investigator should complete Treatment Discontinuation Visit as early as they can after patients formally withdrawal from study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

d. Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months (±7 days) after treatment discontinu ation until death, loss to follow-up, withdrawal of consent or study termination by the Sponsor.

e. Informed consent must be documented before any study-specific screening procedure is performed.

f. Questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

g. Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

h. A twelve-lead ECG and Echocardiogram is required at screening and as clinically indicated thereafter.

i. Includes evaluation of the head, eyes, ears, nose, and throat, superficial lymph node, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

j. Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

k. Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells. Results for full blood count must be available before commencing an infusion (samples must have been obtained within 3 days prior to the infusion, except for C1D1).

l. Chemistry panel (serum or plasma) includes glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. Results for chemistry tests must be available before commencing an infusion (samples must have been obtained within 3 days prior to the infusion, except for C1D1).

m. Only BUN or urea, creatinine, ALT and AST are needed to be performed on day 8 of gemcitabine. Results must be available before commencing an infusion (samples must have been obtained within 3days prior to the infusion, except for C1D1).

n. All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at each cycle during treatment (samples must have been obtained within 3 days prior to the infusion, except for C1D1). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

o. Thyroid function testing (TSH, free T3, free T4) collected at screening, and each cycle thereafter (samples must have been obtained within 3 days prior to the infusion, except for C1D1).

p. Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs). Samples must have been obtained within 3 days prior to the infusion, except for C1D1.

q. All patients will be tested for HCV and HIV prior to the inclusion into the study and HCV-positive and/or HIV-positive patients will be excluded from the clinical trial. HBV DNA must be collected before Cycle 1, Day 1 in patients who have positive serology for hepatitis B surface antigen or negative serology for hepatitis B surface antigen and positive serology for anti-HBc.

r. EBV serology samples will be collected before infusion of C1D1 and every two cycles prior to the infusion for 12 months and then every 3 cycles prior to the infusion until disease progression, loss of clinical benefit, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first; See Appendix 2 for detailed schedule.

s. Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRIs of the nasopharynx, neck, chest and abdomen. A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

t. Tumor assessment should be done to evaluate the target, non-target, and new lesions, it will include all known sites of disease documented at screening, which include but not limit to CT scans (with oral/IV contrast unless contraindicated) or MRIs of the nasopharynx, neck, chest and abdomen, and the same radiographic procedure should be used throughout the study, bone scans should also be performed if clinically indicated. Perform every 6 weeks (±7 days; approximately every two cycles) for 12 months following Cycle 1, Day 1 and then every 9 weeks (±7 days) thereafter, regardle ss of treatment delays, until disease progression, loss of clinical benefit, withdrawal of consent, initiation of new anti-cancer therapy, death, or study termination by the Sponsor, whichever occurs first. CT scans may be repeated at any time if progressive disease is suspected.

u. See Appendix 2 for detailed schedule.

v. See Appendix 2 for detailed schedule.

w. Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug to the treatment discontinuation visit. Subjects receiving anticonvulsants should undergo frequent assessments of their serum level to ensure that a therapeutic concentration is maintained.

x. After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 60 days after the last dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

12.2 Appendix 2 Schedule of Biomarker and Anti-drug Antibody Samples

Period	Timepoint	Visit	Sample type	Volume of Whole Blood
Screening (Day −28 to Day −1)	NA	Screening	Tumor tissue specimen (blocks or 8 or more FFPE slides preferred, if available). Fresh or archival tissue can be used.	NA
During the first year	Pre-dose (same day as treatment administration)	Day 1 of every 2 cycles from C1D1	EBV serology	3 mL
		Day 1 of every 2 cycles from C1D1	Biomarkers	10 mL
		Day 1 of every 4 cycles from C1D1	JS001 ADA and trough concentration	3 mL
After the first year	Pre-dose (same day as treatment administration)	Day 1 of every 3 cycles	EBV serology	3 mL
		Day 1 of every 6 cycles	Biomarkers	10 mL
		Day 1 of every 8 cycles	JS001 ADA and trough concentration	3 mL
At time of initial disease progression	NA	NA	EBV serology	3 mL
			Biomarkers	10 mL
			Tumor tissue specimen, biopsy (optional)*	NA
At time of JS001 discontinuation	NA	NA	JS001 ADA and trough concentration	3 mL

ADA= anti-drug antibody; NA= not applicable

* preferably within 40 days of radiographic progression or prior to start of the next anti-cancer treatment, whichever is sooner.

12.3 Appendix 3 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status Criteria	
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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

12.4 Appendix 4 The Response Evaluation in Solid Tumors (RECIST version 1.1) Guidelines

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

1 Inclusion Criteria

Only subjects with measurable tumors at baseline can be enrolled into the trial protocol with objective tumor response rate as the primary endpoint.

2 Definition

Measurable Disease—At least 1 measurable lesion. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: 10 mm by CT scan (CT scan slice thickness no greater than 5 mm); 10 mm caliper measurement by clinical exam (when superficial); 20 mm by chest X-ray (if clearly defined). Malignant lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Non-measurable Disease—All other lesions, including small lesions (longest diameter > 10 mm or pathological lymph node short axis ≥ 10 to <15 mm) and really non-measurable lesions. Lesions that are deemed as really non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly that is not measurable by reproducible imaging techniques.

Exceptions of Measurable Disease: Including bone lesions, cystic lesions and lesions with prior local treatment. Bone scan, PET scan, or X-ray plain films cannot be used for measurement of bone lesions, but can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. If non-cystic lesions and cystic lesions coexist, non-cystic lesions are preferred for selection as target lesions. Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

All measurements should be recorded in metric notation, using rulers or calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

3 Measurement Methods

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

CT and MRI are the best currently available and reproducible methods to measure target lesions. Conventional CT and MRI use a continuous ≤ 10 mm thick layer. Spiral CT uses 5 mm thick layer for continuous reconstruction algorithm. This standard is suitable for thoracic, abdominal and pelvic tumors, while head and neck tumors and extremity tumors usually require special schemes.

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

Ultrasound (US) should not be used as a method of measurement of tumor lesion when the primary endpoint of the trial is objective response evaluation. The method is not readily accepted in clinical practice. This method can be used as an alternative method to clinically measure superficially palpable lymph nodes, subcutaneous lesions and thyroid nodules. US approach can also be used to confirm the complete disappearance of superficial lesions that are usually evaluated by clinical examination.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in complete response if all tumor lesions disappear. Elevations of tumor markers must be accompanied by visible disease progression to meet the requirements of disease progression.

In a few cases, **cytology and histology** can be used to differentiate between PR and CR (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

When effusions are known to be a potential adverse effect of treatment, the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

4 Tumor Response Evaluation

4.1 "Target" and "Non-target" Lesions Recorded at Baseline

- All measurable lesions, up to 2 lesions in each organ, the sum of up to 5 lesions, and representing all the organs involved as **target lesions**, are recorded and measured at baseline.

- The selection of target lesions should be based on the size (lesions with a maximum diameter) and suitability, so that they can be (by imaging techniques or clinically) accurately and repeatedly measured.

- Calculate the sum of the **longest diameter** (LD) of all target lesions, and report it as baseline sum LD. Use baseline sum LD as a reference value for description of objective tumor.

- All other lesions (or sites of disease) should be used as non-target lesions and reported at baseline. These lesions are not required to be measured, but the presence or absence of each lesion during the entire follow-up period should be recorded.

4.2 Criteria for Response

Criteria for Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum LD.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Criteria for Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/SD:	Persistence of ≥ 1 non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of ≥ 1 new lesions and/or unequivocal progression of existing non-target lesions.*

* Although unequivocal progression of "non-target" lesions is an exception, the opinion of the treating doctor should be referred to, and the progression status later should be confirmed.

4.3 Criteria for Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (the minimum measurements recorded from the start of the treatment should serve as reference values for PD). The subject's best overall response will generally depend on the completion of two measurements and the confirmation criteria.

When the treatment is required to be discontinued due to overall deterioration of the health status, and there is no objective evidence indicating disease progression, the subject should be reported as "symptomatic deterioration." Objective progression should be recorded as far as possible, even after cessation of the treatment.

In some cases, it is difficult to distinguish residual lesion from normal tissue apart. When the evaluation of complete response depends on this decision, it is advised to study the residual lesion (fine needle extraction/biopsy) to confirm the complete response status.

Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD

Any	PD	Yes or No	PD
Any	Any	Yes	PD

12.5 Appendix 5 Immuno-Related Response Evaluation in Solid Tumors (irRECIST)

The text below was obtained from the following reference: Bohnsack O, Hoos A, and Ludajic K. Adaptation of the immune related response criteria: irRECIST. *Annals of Oncology*. 2014.25 (suppl_4): iv361-iv372.

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.

irRC and WHO criteria	**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	**1.1. Baseline: Non-measurable Lesion Definitions**	Although irRC does not specifically define non-target lesions, irRC is derived from

irRC and WHO criteria	irRECIST Modifications and Clarifications	Rationale for Modification
There are many forms of unmeasurable disease, and only a few are mentioned as examples: 1. Lymphangitic pulmonary metastases. 2. Skin involvement in breast cancer. 3. Abdominal masses that can be palpated but not measured.	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 perpendicular 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.	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 selected 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** 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

irRC and WHO criteria	irRECIST Modifications and Clarifications	Rationale for Modification
		protocol definition, indication, and study design.
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 subjects 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 subjects 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.	**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 measurable lesions) are combined into TMTB at follow-up.
	2.1 Follow-up: Definition of Measurable New Lesions	Proposed selection of up to 5 new measurable lesions of at least 10 mm each versus 10 new

irRC and WHO criteria	irRECIST Modifications and Clarifications	Rationale for Modification
	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.	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 subject. 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 lesions 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.
Non-index lesions at follow-up time points 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	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 and WHO criteria	irRECIST Modifications and Clarifications	Rationale for Modification
	leads to an overall assessment of irPD for the time point. Persisting new non-measurable lesions prevent irCR.	
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	**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 subject 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 subjects 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.

12.6 Appendix 6 New York Heart Association Cardiac Function Classification

New York Heart Association Function Classification	
Class	**Symptoms**
1	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
2	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
3	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
4	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

12.7 Appendix 7 Body Surface Area Calculation Formula

BSA (m^2) = SQRT ([Height(cm) × Weight(kg)]/ 3600)

Note: BSA=body surface area; SQRT =square root, H=height; W=weight.

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

12.8 Appendix 8 Method for Calculation of Creatinine Clearance Rate

For men, CrCL (mL/min) = [140- age (years)] ×[weight (kg) [1]]/(72) ×[serum creatinine (mg/dL)]

For women, CrCL (mL/min) = (0.85) ×[140 - age (years)] ×[weight (kg) **[1]**]/(72) ×[serum creatinine (mg/dL)]

For SI unit:

For men, CrCL (mL/min) = [140- age (years)] ×[weight (kg) **[1]**] ×(1.23)/[serum creatinine (μmol/L)]

For women CrCL (mL/min) = [140- age (years)] ×[weight (kg) **[1]**] ×(1.05)/[serum creatinine (μmol/L)]

[1] If the subject is obese (30% over ideal body weight), use the ideal body weight to calculate CrCL

Male: ideal body weight (kg) = height (cm) - 105

Female: ideal body weight (kg) = height (cm) – 100

12.9 Appendix 9 EORTC QLQ-C30 (version 3)

ENGLISH

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): 31

	Not at All	A Little	Quite a Bit	Very Much
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 need 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 a Bit	Very Much
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

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
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 during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

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12.10 Appendix 10 EORTC QLQ - H&N35

ENGLISH

EORTC QLQ - H&N35

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.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

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12.11 Appendix 11 Preexisting Autoimmune Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

Acute disseminated encephalomyelitis	Dermatomyositis	Neuromyotonia
Addison's disease	Diabetes mellitus type 1	Opsoclonus myoclonus syndrome
Ankylosing spondylitis	Dysautonomia	Optic neuritis
Antiphospholipid antibody syndrome	Epidermolysis bullosa acquista	Ord's thyroiditis
Aplastic anemia	Gestational pemphigoid	Pemphigus
Autoimmune hemolytic anemia	Giant cell arteritis	Pernicious anemia
Autoimmune hepatitis	Goodpasture's syndrome	Polyarteritis nodusa
Autoimmune hypoparathyroidism	Graves' disease	Polyarthritis
Autoimmune hypophysitis	Guillain-Barrésyndrome	Polyglandular autoimmune syndrome
Autoimmune myocarditis	Hashimoto's disease	Primary biliary cirrhosis
Autoimmune oophoritis	IgA nephropathy	Psoriasis
Autoimmune orchitis	Inflammatory bowel disease	Reiter's syndrome
Autoimmune thrombocytopenic purpura	Interstitial cystitis	Rheumatoid arthritis
Behcet's disease	Kawasaki's disease	Sarcoidosis
Bullous pemphigold	Lambert-Eaton myasthenia syndrome	Scleroderma
Chronic fatigue syndrome	Lupus erythematosus	Sjögren's syndrome
Chronic inflammatory demyelinating polyneuropathy	Lyme disease - chronic	Stiff-Person syndrome
Chung-Strauss syndrome	Meniere's syndrome	Takayasu's arteritis
Crohn's disease	Mooren's ulcer	Ulcerative colitis
	Morphea	Vitiligo
	Multiple sclerosis	Vogt-Kovanagi-Harada disease
	Myasthenia gravis	Wegener's granulomatosis

12.12 Appendix 12 Anaphylaxis Precautions

Equipment Needed

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

Procedures

In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations

12.13 Appendix 13 Management of Immune-related Adverse Events

From:

Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018 Jun 10;36(17):1714-1768. Link: http://ascopubs.org/doi/full/10.1200/JCO.2017.77.6385

ASCO® Guidelines

MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS IN PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITOR THERAPY: AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLINICAL PRACTICE GUIDELINE

1.0 SKIN TOXICITY

1.1 Rash/Inflammatory Dermatitis Definition: Erythema multiforme minor (a targetoid reaction in the skin and mucous membranes usually triggered by infections, such as Herpes Simplex Viruses, but can be associated with an immune-related drug eruption and if progresses to EM major, it and can be a harbinger of SCAR, such as SJS), lichenoid (resembling the flat-topped, polygonal and sometimes scaly or hypertrophic lesions of lichen-planus), eczematous (Inflammatory dermatitis characterized by pruritic, erythematous, scaly or crusted papules or plaques on the skin, which is vulnerable to superinfection, psoriasiform (resembling the well-demarcated, erythematous and scaly papules and plaques of psoriasis), morbilliform (a non-pustular, non-bullous measles-like exanthematous rash of the skin often referred to as "maculopapular" and without systemic symptoms or lab abnormalities excluding occasional isolated peripheral eosinophilia, Palmoplantar erythrodysaesthesia (PPE) (hand-foot syndrome)

(redness, numbness/burning/itching and superficial desquamation of the palms and soles), neutrophilic dermatoses (e.g. sweet's syndrome) and others.

Diagnostic Workup:

- Pertinent history and physical exam
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug or a skin condition linked to another systemic disease or unrelated primary skin disorder
- If needed, a biological checkup including a blood cell count, liver and kidney tests

• Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody test, SS- A/Anti-Ro, SS-B/Anti-La if predominantly photodistributed/photosensitivity, anti-histone, ds-DNA and other relevant serologies. Consider expanding serologic studies or diagnostic work up if other autoimmune conditions are considered based on signs, symptoms. • Skin biopsy • Consider clinical monitoring with use of serial clinical photography • Review full list of patient medications to rule out other drug-induced cause for photosensitivity	
Grading Grading according to CTCAE criteria is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.	**Management**
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	• Continue immune checkpoint inhibitor (ICPi) • Treat with topical emollients and/or mild-moderate potency topical corticosteroids • Counsel patients to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis.	• Consider holding ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 • Consider initiating prednisone (or equivalent) at dosing 1 mg/kg tapering over at least 4 weeks • In addition, treat with topical emollients, oral antihistamines and medium-to-high potency topical corticosteroids
G3: As grade 2 but with failure to respond to indicated interventions for	• Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming

a grade 2 dermatitis.	• Treat with topical emollients, oral antihistamines and high potency topical corticosteroids • Initiate oral prednisone or equivalent (0.5-1 mg/kg/day) tapering over at least 4 weeks
G4: All severe rashes unmanageable with prior interventions and intolerable.	• Immediate hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) 10mg or less. • Systemic steroids: IV methylprednisolone (or equivalent) dosed at 1–2mg/kg with slow tapering when the toxicity resolves • Monitor closely for progression to Severe Cutaneous Adverse Reaction • Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology • Consider alternative antineoplastic therapy over resuming ICPi's if the skin irAE does not resolve to grade 1 or less. • If ICPI's are the patient's only option, consider restarting once these side effects have resolved to a grade 1 level.
1.2 Bullous Dermatoses **Definition:** including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction	
Diagnostic Workup: • Physical exam • Rule out any other etiology of the skin problem, such as an infection, an effect of another drug or a skin condition linked to another systemic disease.	
• If needed, a biological checkup including a blood cell count, liver and kidney tests, consider serum antibody tests to rule out bullous pemphigoid or, under the guidance of dermatology, sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases	

• Referral to dermatology for blisters that are not explained by infectious or transient other causes (e.g. herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister, etc.) • Consider skin biopsy (both H+E evaluation of lesional skin and direct immunofluorescence evaluation of peri-lesional skin),	
Grading	**Management**
G1: Asymptomatic, Blisters Covering < 10% BSA and no associated erythema	• If blisters are <10% BSA, are asymptomatic and non-inflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary and only observation/local wound care is warranted. • When symptomatic bullae or erosions, which are "deroofed" vesicles or bullae, are noted on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least grade 2 • See grade 2 management recommendations.
G2: Blistering that affects quality of life and require intervention based on diagnosis not meeting criteria for >grade 2. Blisters covering 10%-30% BSA.	• Hold ICPi therapy and consult with dermatology for work up and to determine appropriateness of resuming • Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has "popped" or if the roof of the blister easily sloughs off. • Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens • Workup for autoimmune bullous disease as above • Initiate class 1 high potency topical steroid, eg: clobetasol, betamethasone or equivalent and reassess every 3 days for progression or improvement. • Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks. • Monitor patients with grade 2 irAE's closely for progression to involvement of greater body surface area and/or mucous

	membrane involvement. Consider following patients closely using serial photography. • Primer on monitoring for complicated cutaneous adverse drug reactions: o Review of Systems: Skin pain ("like a sunburn"), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area or pain with bowel movements. o Physical Exam: Include vital signs and a full skin exam specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of drug-induced hypersensitivity syndrome/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema" which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachement of the epidermis to the dermis, which is the case in some autoimmune disorders (e.g. pemphigus) and SJS/TEN.
G3: Skin sloughing covering >30% BSA with associated pain and limiting self care activity of daily living (ADL)	• Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming • Administer IV methylprednisolone (or equivalent) 1-2 mg/kg tapering over at least 4 weeks • If bullous pemphigoid is diagnosed, it may be possible to avoid longterm use of systemic steroids and treat with rituximab, as an alternative approach to treating the irAE. • Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk.

G4: Blisters covering >30% BSA with associated fluid or electrolyte abnormalities	• Permanently discontinue ICPi • Admit patient immediately and place under supervision of a dermatologist • Administer IV methylprednisolone (or equivalent) 1–2mg/kg with tapering over at least 4 weeks when the toxicity resolves • If bullous pemphigoid is diagnosed, it may be possible to avoid long term use of systemic steroids and treat with rituximab, as an alternative approach to treating the irAE. • Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors such as neutropenia etc.

1.3 Severe Cutaneous Adverse Reactions (SCAR), including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS)/Drug-induced Hypersensitivity Syndrome (DIHS)

Definition: Severe changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug

Diagnostic Workup:

- Total body skin exam with attention to examining ALL mucous membranes, as well as complete review of systems Rule out any other etiology of the skin problem,
- such as an infection, an effect of another drug or a skin condition linked to another systemic disease. A biological checkup including a complete blood count (CBC) with differential test (DIFF), liver and kidney function tests, including urinalysis (UA) in addition to the blood work. If the patient is febrile, blood cultures should be considered, as well.
- Skin biopsies to assess for full thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as acute generalized exanthematous pusulosis (AGEP)
- Consider following patients closely using serial clinical photography
  If mucous membrane involvement or blistering is noted on the skin, consider early admission to a burn center for further monitoring and management.
- Primer on monitoring for complicated cutaneous adverse drug reactions:
  - Review of Systems: Skin pain (“like a sunburn”), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia,

hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area or pain with bowel movements.

- Physical Exam: Include vital signs and a full skin exam specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of drug-induced hypersensitivity syndrome/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema" which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (e.g. pemphigus) and SJS/TEN.

Grading	**Management**
All Grades	In cases of suspected SJS or any mucous membranes involvement, discontinue ICPi treatment and monitor closely for improvement regardless of grade.
G1: N/A	• For the SCAR adverse reactions, there is not a grade 1 category. If lower body surface area is involved with bullae or erosions, there should remain high concern that this reaction will progess to grade 3 or 4.
G2: Morbilliform ("maculopapular") exanthem covering 10-30% BSA with systemic symptoms, lymphadenopathy or facial swelling	• Hold ICPi and monitor patients closely every 3 days with grade 2 irAE's for progression to involvement of greater body surface area and/or mucous membrane involvement. • Consider following patients closely using serial photography. • Initiate therapy with topical emollients, oral antihistamines and medium-to-high strength topical corticosteroids • Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks

G3: Skin sloughing covering <10% BSA with mucosal involvement associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	• Hold ICPi therapy and consult with dermatology • Treat skin with topical emollients and other petrolatum emollients, oral antihistamines and high strength topical corticosteroids. Dimethicone may also be offered as an alternative to petrolatum • Administer IV methylprednisolone (or equivalent) 0.5 -1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks • Admit to burn and/or consult wound services with attention to supportive care including fluid and electrolyte balance, minimizing insensible water losses and preventing infection. • Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered. • For mucous membrane involvement of SJS or toxic epidermal necrolysis (TEN), appropriate consulting services should be offered to guide management in preventing sequelae from scarring (e.g. ophthalmology, eyes nose and throat, urology, gynecology, etc. as appropriate)
G4: Skin erythema and blistering/sloughing covering ≥10 to > 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (e.g. LFT elevations in the setting of DRESS/DIHS)	• Permanently discontinue ICPi • Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services. Consider further consultations based on management of mucosal surfaces (e.g. ophthalmology, urology, gynecology, Ear, Nose and Throat Surgery, etc.) • Initiate IV methylprednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal • IVIG or cyclosporine may also be considered in severe or steroid-unresponsive cases • Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations

Additional Considerations:

*The usual prohibition of corticosteroids for Stevens-Johnson Syndrome is not relevant here, as the underlying mechanism is a T-cell immuno- directed toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/Drug Hypersensitivity Syndrome.

2.0 GASTOINTESTINAL TOXICITY

2.1 Colitis

Definition: A disorder characterized by inflammation of the colon.

Diagnostic Workup:

G2:

- Work up of blood (CBC, CMP, TSH, ESR, CRP), stool (culture, C. diff, parasite, CMV or other viral etiology, O&P, should be performed
- Consider testing for lactoferrin (for patient stratification to determine who needs more urgent endoscopy) and calprotectin (to follow up on disease activity)
- Screening labs (HIV, hepatitis A and B, and blood quantiferon for TB) to prepare patients to start infliximab should be routinely done in patients at high risk for those infections and appropriately selected patients based on Infectious disease expert's evaluation
- Imaging e.g. CT scan of abdomen and pelvis and GI endoscopy with biopsy should be considered as there is evidence showing the presence of ulceration in the colon can predict steroid refractory course, which may require early infliximab
- Consider repeating endoscopy for patients who do not respond to immunosuppressive agents. Repeating endoscopy for disease monitoring can be considered when clinically indicated and when planning to resume therapy.

G3-4:

- All the work up listed for G2 (blood, stool, imaging and scope with biopsy) should be completed immediately
- Consider repeating endoscopy for patients who do not respond to immunosuppressive agents. Repeating endoscopy for disease monitoring should only be considered when clinically indicated and when planning to resume ICPi.

Grading	Management

(Based on CTCAE for diarrhea, as most often used clinically)	
All Patients	Counsel all patients to be aware of and inform their healthcare provider immediately if they experience: • abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits • fever, abdominal distention, obstipation, constipation • For Grade ≥2, consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to Grade ≤1; concurrent immunosuppressant maintenance therapy should be considered only if clinically indicated in individual cases
G1: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	• Continue ICPi. Alternatively, ICPi may be held temporarily and resumed if toxicity does not exceed grade 1 • Monitor for dehydration and recommend dietary changes • Facilitate expedited phone contact with patient/caregiver • May obtain gastroenterology consult for prolonged G1 cases
G2: Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	• Should hold ICPi temporarily until patient's symptoms recover to G1. Can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to Grade ≤1. • Concurrent immunosuppressant maintenance therapy (<10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases. • May also include supportive care with medications such as Imodium if infection has been ruled out • Should consult with gastroenterology for G≥2 • Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent. • When symptoms improve to grade 1 or less, taper corticosteroids over at least 4-6 weeks before resuming treatment, although resuming treatment while on low dose corticosteroid may also be an option after an evaluation the risks and benefits

	• EGD/colonoscopy, endoscopy evaluation should be highly recommended for cases grade ≥ 2 to stratify patients for early treatment of infliximab based on the endoscopic findings and to determine the safety of resuming PD-1, PD-L1 therapy. • Stool inflammatory markers can be considered (lactoferrin and calprotectin) in cases grade ≥ 2 to differentiate functional vs inflammatory diarrhea, and use calprotectin to monitor treatment response if provider prefers • Repeat colonoscopy is optional for cases grade ≥ 2 for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICPi
G3: Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	• Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to Grade ≤1. • Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent) • Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance • If symptoms persist ≥3 to 5 days or recur after improvement consider administering intravenous steroid or non-corticosteroid (e.g., infliximab) • Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (i.e., CMV colitis) and for anti-TNF or steroid refractory
G4: Life-threatening consequences; urgent intervention indicated	• Permanently discontinue treatment • Should admit patient when clinically indicated. Patients managed as outpatients should be very closely monitored • Administer 1 to 2 mg/kg/day methylprednisolone or equivalent until symptoms improve to grade 1, and then start taper over 4-6 weeks. • Consider early infliximab 5-10mg/kg if symptoms refractory to steroid within 2-3 days • Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections
Additional Considerations:	

- The use of vedolizumab may be considered in patients refractory to infliximab and/or contraindicated to TNF-a blocker. The decision should be made on an individual basis from gastroenterology and oncology evaluation. This is based on case series showing promising results.[1,2]
- Patients with hepatitis and irAE colitis are rare and management should include permanently discontinuing ICPi and offering other immunosuppressant agents that work systemically for both conditions.
- Currently enteritis alone as the cause of diarrhea is uncommon, and requires small bowel biopsy as the evaluation tool. It may be managed similar as colitis including steroid and/or infliximab etc.

2.2 Hepatitis

Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma

Diagnostic Workup:

- Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin prior to each infusion and/or weekly if Grade 1 LFT elevations. No treatment is recommended for Grade 1 LFT abnormality.

For Grade ≥2:

- Work up for other causes of elevated liver enzymes should be tested, viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, cross- sectional imaging for potential liver metastasis from primary malignancy. If suspicion for primary autoimmune hepatitis is high, can consider ANA/ASMA/ANCA. If patients with elevated ALKP alone, GGT should be tested. For isolated elevation of transaminases, consider checking Creatine Kinase for other etiologies.

Grading	Management
All Patients	• Counsel all patients to be aware of and inform their healthcare provider immediately if they experience • Yellowing of skin or whites of the eyes • Severe nausea or vomiting • Pain on the right side of the abdomen • Drowsiness • Dark urine (tea colored) • Bleeding or bruising more easily than normal • Feeling less hungry than usual

G1: Asymptomatic (AST or ALT >ULN to 3.0x ULN and/or total bilirubin >ULN to 1.5x ULN)	• Continue ICPi with close monitoring; consider alternate etiologies • Monitor labs 1 to 2 times weekly • Manage with supportive care for symptom control
G2: Asymptomatic (AST or ALT >3.0 to ≤5x ULN and/or total bilirubin >1.5 to ≤3x ULN)	• Hold ICPi temporarily and resume if recover to ≤ Grade 1 on prednisone ≤ 10mg/day • For grade 2 hepatic toxicity with symptoms, may administer steroid 0.5-1 mg/kg day prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3-5 days • Increase frequency of monitoring to every 3 days • Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: no clear evidence showing the liver toxicity from infliximab from other studies) • In follow-up, may resume ICPi treatment follow by taper only when symptoms improve to grade 1 or less and steroid ≤ 10mg/day. Taper over at least 1 month. Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs
G3: Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis (AST or ALT 5-20x ULN and/or total bilirubin 3-10 ULN)	• Permanently discontinue ICPi • Immediately start steroid 1-2 mg/kg methylprednisolone or equivalents • If steroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using Azathioprine should test for thiopurine methyltransferase (TPMT) deficiency) • Labs at daily/qod; consider inpatient monitoring for patients with AST/ALT > 8 ULN and/or elevated TB 3 ULN • Increase frequency of monitoring to every 1 to 2 days • Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: no clear evidence showing the liver toxicity from infliximab from other

	studies). Alternatives include non TNFα agents as systemic immunosuppressants • If no improvement is achieved with steroid or for patients on combination therapy with a novel agent, with standard chemotherapy or with targeted therapy refer to hepatologist for further pathologic evaluation of hepatitis • Steroid taper can be attempted around 4-6 weeks, re-escalate if needed, optimal duration unclear
G4: Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma) (AST or ALT >20x ULN and/or total bilirubin >10x ULN)	• Permanently discontinue ICPi • Administer 2 mg/kg/day methylprednisolone equivalents • If steroid refractory or no improvement after 3 days, consider mycophenolate mofetil • Monitor labs daily; Consider inpatient monitoring • Avoid the use of infliximab in the situation of immune-mediated hepatitis • Hepatology consult if no improvement was achieved with steroid • Steroid taper can be attempted around 4-6 weeks when symptoms improve to ≤G1, re-escalate if needed, optimal duration unclear • Consider transfer to tertiary care facility if necessary
3.0 LUNG TOXICITY	
3.1 Pneumonitis **Definition**: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging). No symptomatic, pathologic or radiographic features are pathognomonic for pneumonitis	
Diagnostic Workup • Should include the following: CXR, CT, pulse oximetry; • For G2 or higher, may include the following infectious workup: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity	
Grading	**Management**

G1: Asymptomatic; confined to one lobe of the lung or less than 25% of lung parenchyma; clinical or diagnostic observations only	• Hold ICPi with radiographic evidence of pneumonitis progression • May offer one repeat CT in 3-4 weeks. In patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks • May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 • Monitor patients weekly with history and physical examination, pulse oximetry; may also offer CXR
G2: Symptomatic; Involves more than one lobe of the lung or 25-50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL	• Hold ICPi until resolution to grades ≤1 • Prednisone 1-2 mg/kg/day and taper by 5-10 mg/week over 4-6 weeks • Consider bronchoscopy with BAL • Consider empiric antibiotics • Monitor Q3 days with history and physical examination, pulse oximetry, consider CXR; No clinical improvement after • 48-72 hours of prednisone, treat as grade 3.
G3: Severe symptoms; Hospitalization required: Involves all lung lobes or > 50% of lung parenchyma; limiting self care ADL; oxygen indicated.	• Permanently discontinue ICPi • Empiric antibiotics; (methyl)prednisolone IV 1-2 mg/kg/day; No improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g BID or IVIG X 5 days or cyclophosphamide. Taper corticosteroids over 4-6 weeks • Pulmonary and infectious disease consults if necessary • Bronchoscopy with BAL +/- transbronchial biopsy • Patients should be hospitalized for further management
G4: Life-threatening respiratory compromise; urgent intervention indicated (intubation)	
Additional Considerations: • GI and pneumocystis prophylaxis with PPI and Bactrim may be offered to patients on prolonged steroid use (>12 weeks), according to institutional guidelines[3-6] • Consider calcium and vitamin D supplementation with prolonged steroid use • The role of prophylactic fluconazole with prolonged steroid use (>12 weeks) remains unclear and physicians should proceed according to institutional guidelines[7]	

- Bronchoscopy + Biopsy – if clinical picture is consistent with pneumonitis, no need for biopsy

4.0 ENDOCRINE TOXICITY

- Counsel patients to inform their healthcare provider immediately if they experience any changes in their health since their last visit, especially any of the following:
- Headaches that will not go away or unusual headache patterns
- Vision changes
- Rapid heartbeat
- Increased sweating
- Extreme tiredness or weakness
- Muscle aches
- Weight gain or weight loss
- Dizziness or fainting
- Feeling more hungry or thirsty than usual
- Hair loss
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- Feeling cold
- Constipation
- Voice gets deeper
- Urinating more often than usual
- Nausea or vomiting
- Abdominal pain

4.1 THYROID

4.1.1 Primary Hypothyroidism

Definition: Elevated TSH, normal or low FT4

Diagnostic Workup:

TSH and FT4 every 4-6 weeks as part of routine clinical monitoring on therapy or for case detection in symptomatic patients

Grading	**Management**

G1: TSH <10 mIU/L and asymptomatic	• Should continue ICPi with close follow-up and monitoring of TSH, fT4
G2: Moderate symptoms, Able to Perform ADL. TSH persistently >10 mIU/L	• May hold ICPi until symptoms resolve to baseline • Consider endocrine consultation • Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist over 10 mIU/L (measured 4 weeks apart). • Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH. • FT4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low. • Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active ICPi therapy or as needed for symptoms to ensure appropriate replacement. Repeat testing annually or as indicated by symptoms • once stable
G3-4: Severe symptoms, medically significant or life-threatening consequences, Unable to Perform ADL	• Hold ICPi until symptoms resolve to baseline with appropriate supplementation • Endocrine consultation • May admit for IV therapy if signs of myxedema (bradycardia, hypothermia). • Thyroid supplementation and reassessment as in G2
Additional Considerations • For patients without risk factors, full replacement can be estimated with an ideal body weight based dose of approximately 1.6mcg/kg/day. • For elderly or fragile patients with multiple comorbidities, consider titrating up from low dose, starting at 25-50mcg. • Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic patients to determine whether there is recovery to normal within 3-4 weeks	

- Under guidance of endocrinology, consider tapering hormone replacement and retesting in patients with a history of thyroiditis (initial thyrotoxic phase).
- Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated.

4.1.2 Hyperthyroidism

Definition: Suppressed TSH and high normal or elevated FT4 and/or T3.

Diagnostic Workup:

- Monitor TSH, free T4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients.
- Consider TSH receptor antibodies if there are clinical features and suspicion of Grave's disease (e.g. ophthalmopathy).
- Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism.

Grading	Management
G1: Asymptomatic or mild symptoms	• Can continue ICPi with close follow-up and monitoring of TSH, fT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see 4.1.1).
G2: Moderate symptoms, Able to Perform ADL	• Consider holding ICPi until symptoms return to baseline • Consider endocrine consultation • Beta-blocker (e.g. atenolol or propranolol) for symptomatic relief. • Hydration and supportive care • Corticosteroids are not usually required to shorten duration. • For persistent hyperthyroidism (>6 weeks) or clinical suspicion, work up for Graves' disease (TSI or TRAb) and consider thionamide (methimazole or PTU). • Refer to Endocrinology for Graves' disease.

G3-4: Severe symptoms, medically significant or life-threatening consequences, Unable to Perform ADL	• Hold ICPi until symptoms resolve to baseline with appropriate therapy • Endocrine consultation • Beta-blocker (e.g. atenolol or propranolol) for symptomatic relief. • For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2mg/kg/day or equivalent tapered over 1-2 weeks. Consider also use of SSKI or thionamide (methimazole or PTU).

Additional Considerations:

- Thyroiditis is transient and resolves in a couple of weeks to primary hypothyroidism or normal. Hypothyroidism can be treated as above.
- Graves' disease is generally persistent and is due to increased thyroid hormone production that can be treated with anti-thyroid medical therapy.
- Physical exam findings of ophthalmopathy or thyroid bruit are diagnostic of Graves and should prompt early Endocrine referral.

4.2 Adrenal - Primary adrenal insufficiency (AI)

Definition: Adrenal gland failure leading to low morning cortisol, high morning ACTH as well as hyponatremia and hyperkalemia with orthostasis and volume depletion due to loss of aldosterone.

Diagnostic Workup for patients in whom adrenal insufficiency is suspected:

- Evaluate ACTH (AM), cortisol level (AM)
- Basic Metabolic Panel (Na, K, CO2, Glucose)
- Consider ACTH stimulation test for indeterminate results
- If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically:
    - Evaluate for precipitating cause of crisis such as infection
    - Adrenal CT for metastasis/hemorrhage

Grading	Management
G1: Asymptomatic or mild symptoms	• Consider holding ICPi until patient is stabilized on

	replacement hormone. • Endocrine consultation • Replacement therapy with prednisone (5-10mg daily) or hydrocortisone (10-20mg po qAM, 5-10mg po q2PM) • May require fludrocortisone (0.1mg/day) for mineralocorticoid replacement in primary adrenal insufficiency. • Titrate dose up or down as symptoms dictate
G2: Moderate symptoms, Able to Perform ADL	• Consider holding ICPi until patient is stabilized on replacement hormone. • Endocrine consultation • Initiate outpatient treatment at 2-3 times maintenance (e.g. if prednisone, 20 mg daily; if hydrocortisone 20-30 mg on the morning and 10-20 mg in the afternoon) to manage acute symptoms. • Taper stress dose corticosteroids down to maintenance doses over 5-10 days. • Maintenance therapy as in G1.
G3-4: Severe symptoms, medically significant or life-threatening consequences, Unable to Perform ADL	• Hold ICPi until patient is stabilized on replacement hormone. • Endocrine consultation • See in clinic or, after hours, make an ER referral for: o Normal saline (at least 2L) o IV Stress dose steroids on presentation: Hydrocortisone 100 mg or Dexamethasone 4 mg (if the diagnosis is not clear and stimulation testing will be needed) • Taper stress dose corticosteroids down to maintenance doses over 7-14 days after discharge • Maintenance therapy as in G1

Additional Considerations:

- Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management is as per 4.3
- Patients on corticosteroids for management of other conditions, will have low morning cortisol as a result of iatrogenic, secondary AI. ACTH will also be low in these patients. A diagnosis of AI is challenging to make in these situations (see below section on hypophysitis).
- Emergent therapy for someone with *suspected* AI is best done with dexamethasone as a stimulation test can still be performed. If the diagnosis is already confirmed, can use hydrocortisone 100 mg.
- All patients need education on stress dosing and a medical alert bracelet for adrenal insufficiency to trigger stress dose corticosteroids by EMS.
- Endocrine consultation prior to surgery or any procedure for stress dose planning.

4.3 Pituitary - Hypophysitis

Definition: inflammation of the pituitary with varying impacts on hormone function. Most commonly presenting with central adrenal insufficiency. May also have central hypothyroidism, Diabetes insipidus and hypogonadism

Diagnostic Workup:

Diagnosis: Low ACTH with a low cortisol. Low or normal TSH with a low FT4. Hypernatremia and volume depletion with DI. Low testosterone or estradiol with low LH and FSH.

Testing:

- Evaluate ACTH, cortisol (AM), TSH, free T4, electrolytes.
- Consider evaluating LH, FSH and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido and mood changes
- Consider MRI brain w/wo contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities +/- new severe headaches or complaints of vision changes

Grading	Management

G1: Asymptomatic or mild symptoms	• Considering holding ICPi until patient is stabilized on replacement hormones. • Hormonal supplementation as needed, using dosing as above for primary hypothyroidism and adrenal insufficiency (e.g. hydrocortisone 10-20 mg orally in the morning, 5-10 mg orally in early afternoon; levothyroxine by weight). • Testosterone or estrogen therapy as needed in those without contraindications. • Endocrine consultation • Always start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis • Follow FT4 for thyroid hormone replacement titration (TSH is not accurate).
G2: Moderate symptoms, Able to Perform ADL	• Consider holding ICPi until patient is stabilized on replacement hormones. • Endocrine consultation • Hormonal supplementation as in G1
G3-4: Severe symptoms, medically significant or life-threatening consequences, Unable to Perform ADL	• Hold ICPi until patient is stabilized on replacement hormones. • Endocrine consultation • Hormonal supplementation as in G1 • Consider initial pulse dose therapy with Prednisone 1-2mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks
Additional Considerations: • Please be aware of the need to START CORTICOSTEROIDS FIRST when planning hormone replacement therapy for multiple deficiencies. • All patients need instruction on doubling doses for illness (stress dosing) and a medical alert bracelet for adrenal insufficiency to trigger stress dose corticosteroids by EMS. • Steroid use can cause isolated central adrenal insufficiency.	

- Workup cannot be done with a simple AM cortisol in a patient on corticosteroids for other conditions.
- Laboratory confirmation of AI should not be attempted until treatment with corticosteroids for other disease is ready to be discontinued.
- For long term exposure, consult endocrinology for recovery and weaning protocol using hydrocortisone

4.4 Diabetes

Definition: T2DM is a combination of insulin resistance and insufficiency that may require oral or insulin therapy. It may be new onset or exacerbated during therapy for non-immunologic reasons such as steroid exposure.

Autoimmune T1DM results from islet cell destruction and is often acute onset, with ketosis and an insulin requirement.

Diagnostic Workup:

- Monitor patients for hyperglycemia or other signs and symptoms of new or worsening DM, including measuring glucose at baseline and with each treatment cycle during induction X 12 weeks, then every 3-6 weeks thereafter. To guide the work up in new onset hyperglycemia, clinicians should consider a patient's medical background, exposure history, and risk factors for each subtype of DM.
- Laboratory evaluation in suspected T1DM should include testing for ketosis in urine and an assessment of the anion gap on a metabolic panel. Anti-GAD, anti-Islet Cell or anti-Insulin antibodies are highly specific for autoimmune diabetes. Insulin and c-peptide levels can also assist in the diagnosis.

Grading	Management
G1: Asymptomatic or mild symptoms; Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/LNo evidence of ketosis or laboratory evidence of T1DM	• Can continue ICPi with close clinical follow-up and laboratory evaluation • May initiate oral therapy for those with new onset T2DM. • Screen for T1DM if appropriate for example acute onset with prior normal values or clinical concern for ketosis
G2: Moderate symptoms, Able to Perform Activities of Daily Living; Fasting glucose value >160 - 250 mg/dL; Fasting	• May hold ICPi until glucose control is obtained. • Titrate oral therapy or add insulin for worsening control in T2DM. • Should administer insulin for T1DM (or as default therapy if

glucose value >8.9 - 13.9 mmol/L. Ketosis or evidence of T1DM at any glucose level	there is confusion about type) • Urgent Endocrine consultation for any patient with T1DM. In the absence of endocrinology, internal medicine may suffice • Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present.
G3-4: Severe symptoms, medically significant or life-threatening consequences, Unable to Perform Activities of Daily Living; G3: >250 - 500 mg/dL; >13.9 - 27.8 mmol/L; G4: >500 mg/dL; >27.8 mmol/L	• Hold ICP i until glucose control is obtained on therapy with reduction of toxicity to grade 1 or less. • Urgent Endocrine consultation for all patients. • Initiate insulin therapy for all patients. • Admit for inpatient management: o Concerns for developing DKA o Symptomatic patients regardless of diabetes type o New onset T1DM unable to see Endocrinology.
Additional Considerations: • Insulin therapy can be used as the default in any case with hyperglycemia. • Long acting therapy alone is not usually sufficient for T1DM, where half of daily requirements are usually given in divided doses as prandial coverage and half as long acting. • Insulin doses will be lower in T1DM because of preserved sensitivity (total daily requirement can be estimated at 0.3-0.4 units/kg/day). • In T2DM, sliding scale coverage with meals over a few days provides data to estimate a patient's daily requirements and can be used to more rapidly titrate basal needs.	
5.0 MUSCULOSKELETAL TOXICITY	
5.1 Inflammatory Arthritis **Definition:** A disorder characterized by inflammation of the joints. **Clinical Symptoms:** Joint pain accompanied by joint swelling, inflammatory symptoms such as stiffness after inactivity or in the morning, lasting more than 30 mins-1 hour. Improvement of symptoms with NSAIDs or corticosteroids, but not with opioids or other pain meds may also be suggestive of IA	

Diagnostic Workup:

G1:

- Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling and range of motion. Examination of the spine
- Consider plain X ray/imaging to exclude metastases and evaluate joint damage (erosions) if appropriate
- Consider autoimmune blood panel including ANA, RF, and anti-CCP and anti-inflammatory markers (ESR and CRP) if symptoms persist. If symptoms are suggestive of reactive arthritis or affect the spine consider HLA B27 testing

G2:

- Complete history and examination as above; laboratory tests as above
- Consider US +/- MRI imaging of affected joints if clinically indicated (e.g. persistent arthritis unresponsive to treatment, suspicion for differential diagnoses such as metastatic lesions or septic arthritis)
- Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms persist >4 weeks

G3-4:

- As for Grade 2
- Seek rheumatologist advice and review

Monitoring:

- Patients with inflammatory arthritis should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted

Grading	Management
All Grades	Clinicians should follow reports of new joint pain to determine if IA is present. Question whether symptom new since receiving ICPi.
G1: Mild pain with inflammation, erythema, or joint swelling	• Continue ICPi • Initiate analgesia with acetaminophen and/or NSAIDs

G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	• Hold ICPi and resume upon symptom control and on prednisone ≤ 10mg/day • Escalate analgesia and consider higher doses of NSAIDS as needed • If inadequately controlled, initiate prednisone or prednisolone 10-20 mg/day or equivalent x 4-6 weeks • If improvement, slow taper according to response during the next 4-6 weeks. If no improvement after initial 4-6 weeks treat as G3. • If unable to lower corticosteroid dose to below 10mg/d after 3 months, consider disease-modifying antirrheumatic drug (DMARD) • Consider intra-articular steroid injections for large joints • Referral to rheumatology
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self care ADL	• Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to ≤G1 • Initiate oral prednisone 0.5-1 mg/kg • If failure of improvement after 4 weeks or worsening in meantime – consideration of synthetic or biologic disease-modifying antirrheumatic drug (DMARD) o Synthetic: methotrexate, leflunomide; o Biologic: Consider anti-cytokine therapy such as TNFα or IL6 receptor inhibitors. Note: As caution, IL6 inhibition can cause intestinal perforation. While this is extremely rare, it should not be used in patients with colitis • Test for viral hepatitis B, C and latent/active TB test prior to DMARD treatment • Referral to rheumatology
Additional Considerations: • Early recognition is critical to avoid erosive joint damage	

- Corticosteroids can be used as part of initial therapy in IA, but due to likely prolonged treatment requirements, physicians should consider starting steroid-sparing agents earlier than one would with other irAEs.
- Oligoarthritis can be treated early on with intra-articular steroids, consider early referral
- Consider PCP prophylaxis for patients treated with high dose of corticosteroids for longer than 12 weeks, as per local guidelines

5.2 Myositis

Definition: A disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life- threatening if respiratory muscles or myocardium are involved.

Diagnostic Workup:

- Complete rheumatological and neurological history regarding differential diagnosis and rheumatological and neurological examination including muscle strength, and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider pre-existing conditions that can cause similar symptoms;
- Blood testing to evaluate muscle inflammation
- Creatine kinase (CK), transaminases (AST, ALT), LDH and aldolase can also be elevated
- Troponin to evaluate myocardial involvement, and other cardiac testing such as echocardiogram as needed
- Inflammatory markers (ESR and CRP).
- Consider electromyography (EMG), imaging (MRI) and/or biopsy on an individual basis when diagnosis is uncertain, and overlap with neurologic syndromes such as myasthenia gravis is suspected.
- Consider paraneoplastic autoantibody testing for myositis and neurological conditions such as myasthenia gravis

Monitoring: CK, ESR, CRP

G1: Complete examination and laboratory work-up as above

G2: Complete history and examination as above;
autoimmune myositis blood panel; EMG, MRI imaging of affected joints Early referral to a rheumatologist or neurologist

G3-4: As for Grade 2

Urgent referral to a rheumatologist or neurologist	
Grading	**Management**
G1: Mild weakness with or without pain	• Continue ICPi • If CK is elevated and patient has muscle weakness may offer oral corticosteroids, and treat as grade 2 • Offer analgesia with acetaminophen or NSAIDs if there are no contraindications
G2: Moderate weakness with or without pain limiting age-appropriate instrumental ADL	• Hold ICPi temporarily and may resume upon symptom control, if CK is normal and prednisone dose < 10mg; if worsens, treat as per G3 • NSAIDs as needed • Referral to rheumatologist or neurologist • If CK is elevated (x3 or more), initiate prednisone or equivalent at 0.5-1 mg/kg • May require permanent discontinuation of ICPi in most cases with G2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy).
G3-4: Severe weakness with or without pain; limiting self care ADL	• Hold ICPi until grade ≤1 off immune suppression and permanently discontinue if any evidence of myocardial involvement • Consider hospitalization for severe weakness • Referral to rheumatologist or neurologist • Initiate prednisone 1 mg/kg or equivalent. Consider 1-2mg/kg of methylprednisolone IV or higher dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia). • Consider plasmapheresis • Consider IVIG therapy

	• Consider other immunosuppressant therapy such as methotrexate, azathioprine, or mycophenolate mofetil if symptoms and CK levels do not improve or worsen after 4-6 weeks. Rituximab is used in primary myositis but caution is advised given its long biological duration

Additional Considerations:

- Caution is advised with rechallenging

5.3 Polymyalgia-like Syndrome

Definition: Characterized by marked pain and stiffness in proximal upper and/or lower extremities, and no signs of true muscle inflammation such as CK elevation or EMG findings of myositis . No true muscle weakness, difficulty in active motion related to pain.

Diagnostic Workup:

G1: Complete rheumatological history regarding differential diagnosis and examination of all joints and skin

Check for symptoms of temporal arteritis, such as headache or visual disturbances, refer to ophthalmologist if present, and consider temporal artery biopsy ANA, RF, anti-CCP CK to evaluate differential diagnosis of myositis Inflammatory markers (ESR, CRP)

Monitoring: ESR, CRP

G2: Complete history and examination as above; autoimmune tests as required for differential diagnosis; Early referral to a rheumatologist

G3-4: As for Grade 2

Seek rheumatologist advice and review

Grading	Management
G1: Mild stiffness and pain	• Continue ICPi • Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications
G2: Moderate stiffness and pain ; limiting age-appropriate instrumental ADL	• Consider holding ICPi and resuming upon symptom control, prednisolone < 10mg; if worsens, treat as per G3 • Initiate prednisone 20 mg/d or equivalent. If symptoms improve, start to taper dose after 3-4 weeks.

	• If no improvement or need for higher dosages after 4 weeks, escalate to G3 • Consider referral to rheumatology
G3-4: Severe stiffness and pain; limiting self care ADL	• Hold ICPi and may resume, in consultation with rheumatology, if recover to ≤G1. However, note that cases of toxicity returning upon rechallenge have been reported. • Referral to rheumatology • Should initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a steroid sparing agent such as methotrexate or IL6 inhibition with tocilizumab. Note: As caution, IL6 inhibition can cause intestinal perforation. While this is extremely rare, it should not be used in patients with colitis or GI metastases • Consider admission for pain control
6.0 RENAL TOXICITIES	
Nephritis and Renal Dysfunction – Diagnosis and Monitoring • For any suspected immune-mediated adverse reactions, exclude other causes. • Monitor patients for elevated serum creatinine prior to every dose. • Routine urinalysis is not necessary, other than to rule out UTIs etc. Nephrology may consider further. • If no potential alternative cause of AKI identified, then one should forego biopsy and proceed directly with immunosuppressive therapy. • Swift treatment of autoimmune component important	
6.1 Nephritis **Definition:** Inflammation of the kidney affecting the structure	
Grading	**Management**
G1: Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0x above	• Consider temporarily holding ICPi, pending consideration of potential alternative etiologies (recent IV contrast,

baseline	medications, fluid status) and baseline renal function. A change that is still <1.5 ULN *could* be meaningful
G2: Creatinine 2 - 3x above baseline	• Hold ICPi temporarily • Consult nephrology • Evaluate for other causes (recent IV contrast, medications, fluid status etc.) If other etiologies ruled out, administer 0.5 to 1 mg/kg/day prednisone equivalents • If worsening or no improvement: 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue treatment • If improved to G1 or less taper steroids over 4-6 weeks. • If no recurrence of chronic renal insufficiency discuss resumption of ICPI with patient after taking into account the risks and benefits.
G3: Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated **G4:** Life-threatening consequences; dialysis indicated	• Permanently discontinue ICPi • Consult nephrology • Evaluate for other causes (recent IV contrast, medications, fluid status etc.) • Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent)
Additional Considerations: Monitor creatinine weekly. Reflex kidney biopsy should be discouraged until steroid treatment has been attempted.	
6.2 Symptomatic Nephritis – Follow Up	
Grading	**Management**
G1	If improved to baseline • Resume routine creatinine monitoring
G2	If improved to Grade 1: • Taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring

	If elevations persist > 7 days or worsen and no other cause found, treat as Grade 3
G3	If improved to Grade 1: • Taper corticosteroids over at least 4 weeks If elevations persist > 3-5 days or worsen, consider additional immunosuppression (e.g. mycophenolate)
G4	If improved to Grade 1: • Taper corticosteroids over at least 4 weeks If elevations persist > 2-3 days or worsen, consider additional immunosuppression (e.g. mycophenolate).
7.0 NERVOUS SYSTEM TOXICITY	
7.1 Myasthenia Gravis **Definition: Fatigable** or fluctuating muscle weakness, generally proximal>distal. Frequently has ocular and/or bulbar involvement (ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, dysarthria, facial muscle weakness). May have neck and/or respiratory muscle weakness. Note, may occur with myositis and/or myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis, myocarditis. Miller Fisher variant of Guillain Barre syndrome (ophthalmoparesis) and the oculobulbar myositis (ptosis, ophthalmoparesis, dysphagia, neck and respiratory weakness) with ICPi may have overlapping symptoms.	
Diagnostic Workup: • Acetylcholine receptor (AChR) and anti-striated muscle antibodies in blood. If AChR antibodies are negative, consider muscle specific kinase (MuSK) and lipoprotein related 4 (LPR4) antibodies in blood. • Pulmonary function assessment with NIF (negative inspiratory force) and VC (vital capacity). • CPK, aldolase, ESR, CRP for possible concurrent myositis • Consider MRI brain and/or spine depending on symptoms to rule out CNS involvement by disease or alternate diagnosis • If respiratory insufficiency or elevated CPK, troponin T, perform cardiac exam, EKG and TTE for possible concomitant myocarditis • Neurological consultation • Electrodiagnositic studies including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate	

for myositis.

Grading	Management
All Grades	All grades warrant workup and intervention given potential for progressive MG to lead to respiratory compromise
No G1	
G2: Some symptoms interfering with ADLs MGFA severity class I (ocular symptoms and findings only) and MGFA severity class II (mild generalized weakness).	• Hold ICPi and may resume in G2 patients (MGFA 1 and 2) only if symptoms resolve[8] • Should consult neurology • Pyridostigmine starting at 30 mg PO TID and gradually increase to maximum of 120mg PO QID as tolerated and based on symptoms • Administer corticosteroids (prednisone 1-1.5mg/kg orally daily) if symptoms G2. Wean based on symptom improvement.
G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms. or MGFA Severity Class III-V moderate to severe generalized weakness to myasthenic crisis	• Permanently discontinue ICPi • Admit patient, may need ICU-level monitoring. • Neurology consult • Continue steroids and initiate IVIG 2G/kg IV over 5 days (0.4G/kg/day) or plasmapheresis x 5 days. • Frequent pulmonary function assessment • Daily neurological review

Additional Considerations:

- Avoid medications that can worsen myasthenia: beta-blockers, IV magnesium, fluoroquinolones, aminoglycosides and macrolides
- Initially a 5 day course of plasmapheresis or a 2G/kg course of IVIG over 5 days
- 1-2 mg/kg methylprednisolone daily, wean based on symptom improvement
- Pyridostigmine, wean based on improvement.
- ICPi-associated MG may be monophasic and additional steroid sparing agents may not be required.

7.2 Guillain-Barre Syndrome

Definition: Progressive most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. Often starts with sensory symptoms/neuropathic pain localized to lower back and thighs. May involve extremities (typically ascending weakness but not always), facial, respiratory and bulbar & oculomotor nerves. May have dysregulation of autonomic nerves.

Diagnostic Workup:

- Neurologic consultation
- MRI spine w/wo contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening)
- Lumbar puncture: CSF typically has elevated protein and often elevated WBC as well even though this is not typically seen in classical Guillain-Barre, cytology (should be sent with any CSF sample from a patient with cancer).
- Serum antibody tests for GBS variants (GQ1b for Miller Fisher variant a/w ataxia and ophthalmoplegia)
- Electrodiagnostic studies to evaluate polyneuropathy
- Pulmonary function testing (NIF/VC)
- Frequent neurochecks

Grading	Management
All grades warrant workup and intervention given potential for progressive GBS to lead to respiratory compromise. Note, there is no G1 toxicity.	
G1: Mild: None	NA
G2: Moderate: Some interference with ADLs, symptoms concerning to patient.	• Discontinue ICPi • Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring • Start IVIG (0.4G/kg/day for 5 days for a total dose of 2G/kg) or plasmapheresis. Corticosteroids are usually not recommended for idiopathic GBS, however in ICPi-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/day), followed by slow steroid taper. Pulse steroid dosing (methylprednisolone 1 gram daily for 5 days) may also be considered for G3-4 along with IVIG or plasmapheresis. • Frequent neurochecks and pulmonary function monitoring.

	• Monitor for concurrent autonomic dysfunction • Non opioid management of neuropathic pain Treatment of constipation/ileus
Additional Considerations: • Slow prednisone taper after steroid pulse plus IVIG or plasmapheresis • May require repeat IVIG courses • Caution with rechallenging for severe cases	
7.3 Peripheral Neuropathy **Definition:** Can present as asymmetric or symmetric sensory, motor, or sensory-motor deficit. Focal mononeuropathies including cranial neuropathies (e.g. facial neuropathies/Bell's palsy) may be present. Numbness and paresthesias may be painful or painless. Hypo- or areflexia. Sensory ataxia may be present.	
Diagnostic Workup: **G1:** • Screen for reversible neuropathy causes: diabetic screen, B12, folate, TSH, HIV, consider serum protein electrophoresis, and other vasculitic & autoimmune screen • Neurologic consultation • Consider MRI spine w/wo contrast **G2**: In addition to above: • MRI spine advised/ MRI brain if cranial nerve • Consider EMG/NCS • Consider Neurology consultation **G3-4**: go to Guillain-Barre Syndrome (GBS) algorithm	
Grading	**Management**
G1: Mild: No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate	• Low threshold to hold ICPi and monitor symptoms for a week. If to continue, monitor very closely for any symptom progression.
G2: Moderate: Some interference with ADLs, symptoms concerning to	• Hold ICPi and resume once return to G1 • Initial observation OR initiate prednisone 0.5-1mg/kg (if

patient (i.e. Pain but no weakness or gait limitation).	progressing from mild) • Neurontin, pregabalin, or duloxetine for pain
G3-4: Severe: Limiting self-care and aids warranted, weakness limiting walking or respiratory problems (i.e. leg weakness, foot drop, rapidly ascending sensory changes). Severe may be GBS and should be managed as such.	• Permanently discontinue ICPi • Admit patient • Neurologic consultation • Initiate IV methylprednisolone 2-4 mg/kg and proceed as per GBS management.
G3-4: Severe: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.	
7.4 Autonomic neuropathy **Definition:** Nerves that control involuntary bodily functions are damaged. This may affect blood pressure, temperature control, digestion, bladder function and sexual function. A case of severe enteric neuropathy with ICPi has been reported. Can present with GI difficulties such as new severe constipation, nausea; urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction and orthostatic hypertension.	
Diagnostic Workup: An evaluation by neurologist or relevant specialist depending on organ system, with testing which may include: • Screen for other causes of autonomic dysfunction: diabetic screen, adrenal insufficiency, HIV, paraproteinemia, amyloidosis, botulism, consider chronic diseases such as Parkinson's and other autoimmune screen • AM orthostatic vitals • Consider electrodiagnostic studies to evaluate for concurrent polyneuropathy • Consider paraneoplastic LEMS, ANNA-1 ab, ganglionic acetylcholine receptor ab testing	
Grading	**Management**

G1: Mild: No interference with function and symptoms not concerning to patient.	• Low threshold to hold ICPi and monitor symptoms for a week. If to continue, monitor very closely for any symptom progression.
G2: Moderate: Some interference with ADLs, symptoms concerning to patient	• Hold ICPi and resume once return to G1 • Initial observation OR initiate prednisone 0.5-1mg/kg (if progressing from mild) • Neurological consultation
G3-4: Severe: Limiting self-care and aids warranted	• Permanently discontinue ICPi • Admit patient • Initiate methylprednisolone 1 gram daily x 3 days followed by oral steroid taper • Neurologic consultation
7.5 Aseptic meningitis **Definition:** May present with headache, photophobia, neck stiffness, often afebrile but may be febrile. There may be nausea/vomiting Mental status should be normal (distinguishes from encephalitis)	
Diagnostic Workup: • MRI brain w/wo contrast + pituitary protocol • AM cortisol, ACTH to rule out adrenal insufficiency • Consider lumbar puncture: measure opening pressure, check cell count, protein glucose, gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology • May see elevated WBC with normal glucose, normal culture and gram stain. May see reactive lymphocytes or histiocytes on cytology	
Grading	**Management**
G1: Mild: No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate.	• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits • Consider empiric antiviral (IV acyclovir) and antibacterial therapy until CSF results

G2: Moderate: Some interference with ADLs, symptoms concerning to patient (i.e. Pain but no weakness or gait limitation).	• Once bacterial and viral infection negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1 mg/kg if moderate/severe symptoms.
G3-4: Severe: Limiting self-care and aids warranted	
7.6 Encephalitis **Definition:** *As for aseptic meningitis, need to exclude infectious causes, especially viral (i.e. HSV).* Confusion, altered behavior, headaches, seizures, short term memory loss, depressed level of consciousness, focal weakness, speech abnormality	
Diagnostic Workup: • Neurologic Consultation • MRI brain w/wo contrast may reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal • Lumbar puncture: check cell count, protein glucose, gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology, oligoclonal bands, autoimmune encephalopathy and paraneoplastic panels. • May see elevated WBC with lymphocytic predominance and/or elevated protein • EEG to evaluate for subclinical seizures • Bloods: metabolic, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin • Rule out concurrent anemia/thrombocytopenia, which can present w severe headaches and confusion	
Grading	**Management**
G1: Mild: No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate.	• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits • As above for aseptic meningitis suggest concurrent IV acyclovir until PCR results obtained and negative • Trial of methylprednisolone 1-2 mg/kg • If severe or progressing symptoms or oligoclonal bands
G2: Moderate: Some interference with ADLs,	

symptoms concerning to patient (i.e. Pain but no weakness or gait limitation).	present, consider pulse corticosteroids methylprednisolone 1G IV daily for 3-5 days plus IVIG 2 g/kg over 5 days. • If positive for autoimmune encephalopathy antibody and limited or no improvement, consider Rituximab or plasmapheresis in consultation with neurology
G3-4: Severe: Limiting self-care and aids warranted	
7.7 Transverse Myelitis **Definition:** Acute or subacute weakness or sensory changes bilateral, often with increased deep tendon reflexes	
Diagnostic Workup: • Neurologic consultation • MRI spine (with thin axial cuts through the region of suspected abnormality) and MRI brain • Lumbar puncture: cell count, protein, glucose, oligoclonal bands, viral PCRs, cytology, onconeural antibodies • Bloods: B12, HIV, RPR, ANA, Ro/La, TSH, aquaporin-4 IgG • Evaluation for urinary retention, constipation	
Grading	**Management**
G1: Mild: No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate	• Permanently discontinue ICPi • Methylprednisolone 2 mg/kg • Strongly consider higher doses of 1g/day for 3-5 days • Strongly consider IVIG
G2: Moderate: Some interference with ADLs, symptoms concerning to patient (i.e. Pain but no weakness or gait limitation).	
G3-4: Severe: Limiting self-care and aids warranted	
8.0 AUTOIMMUNE HEMATOLOGIC TOXICITY	
8.1 Hemolytic Anemia **Definition:** A condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over. Symptoms include weakness, paleness, jaundice, dark-colored urine,	

fever, inability to do physical activity, and heart murmur.

Diagnostic Workup:

- History and physical examination (with special consideration of history of new drugs, insect, spider or snake bites)
- Blood chemistry, CBC with evidence of anemia, macrocytosis, evidence of hemolysis on peripheral smear. LDH, haptoglobin, bilirubin, reticulocyte count, free hemoglobin
- DIC panel which could include PT/INR, infectious causes
- Autoimmune serology
- PNH screening
- Direct and indirect bilirubin, LDH, direct agglutinin test, and if no obvious cause, bone marrow analysis, cytogenetic analysis to evaluate MDS
- Evaluation for viral/bacterial (mycoplasma etc.) causes of hemolysis studies
- Protein electrophoresis, cryoglobulin analysis
- Workup for BM failure syndrome if refractory including B12, folate, copper, parvo virus, FE, thyroid, infectious
- Glucose-6-phosphate dehydrogenase
- Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDS, Quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, diclofenac etc)
- Assessment of methemaglobinemia

Grading	Management
G1: Hgb<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	• Continue ICPi with close clinical follow-up and laboratory evaluation
G2: Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	• Hold ICPi and strongly consider permanent discontinuation • Administer 0.5 to 1 mg/kg/day prednisone equivalents

G3: Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	• Permanently discontinue ICPi • Should use clinical judgement and consider admitting the patient • Hematology consult • Prednisone 1-2 mg/kg/day (oral or IV depending on symptoms/speed of development) • If worsening or no improvement, 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue ICPi treatment • Consider RBC transfusion per existing guidelines. Do not transfuse more than the minimum number of red blood cell (RBC) units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g/dL in stable, non-cardiac in-patients) • Should offer patients supplementation with folic acid 1mg QD
G4: Life-threatening consequences; urgent intervention indicated	• Permanently discontinue ICPi • Admit patient • Hematology consult • IV prednisone corticosteroids 1-2 mg/kg/day • If no improvement on or if worsening on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, CSA, infliximab, MMF and ATG • RBC transfusion per existing guidelines. Discuss with blood bank team prior to transfusions that a patient with possible ICPi SAE is in house.
Additional Considerations: • Monitor hemoglobin levels on a weekly basis until the steroid tapering process is complete. Thereafter, less frequent testing is needed.[9]	
8.2 Acquired Thrombotic Thrombocytopenic Purpura **Definition:** A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition	

Diagnostic Workup:

- If no improvement on or if worsening on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, CSA, infliximab, MMF and ATG
- History with specific questions related to drug exposure (e.g. chemotherapy, sirolimus, tacrolimus, Opana ER, antibiotics, quinine,)
- Physical exam, peripheral smear
- ADAMTS13 activity level and inhibitor titer
- LDH, haptoglobin, reticulocyte count, bilirubin, urinalysis to rule out other causes
- Prothrombin time, activated partial thromboplastin time, fibrinogen
- Blood group and antibody screen, direct antiglobulin test, cytomegalovirus serology
- Consider CT/MRI brain, echocardiogram, electrocardiogram Viral studies
- Viral studies
- Note: this disorder is usually associated with severe drop in platelets and hemolysis/anemia precipitously

Grading	Management
All Grades	• The first step in the management of TTP is a high index of suspicion for the diagnosis and timely recognition. Hematology consult should immediately be called, as delay in identification is associated with increased mortality/morbidity. • Initially, the patient should be stabilized and any critical organ dysfunction stabilized.
G1: Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency or thrombocytopenia clinically	• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there is currently no data to recommend restarting ICPi therapy • Hematology consult • Administer 0.5 to 1 mg/kg/day prednisone
G2: Evidence of RBC destruction (schistocytosis) without clinical consequence with G2 anemia and	

thrombocytopenia	
G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, renal insufficiency >2) **G4:** Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there is currently no data to recommend restarting ICPi therapy • Hematology consult • In conjunction with hematology Initiate plasma exchange (PEX) according to existing guidelines with further PEX dependent on clinical progress[10-12] • Administer methylprednisolone 1 g intravenously daily for 3 days, with the first dose typically administered immediately after the first PEX • May offer rituximab
8.3 Hemolytic uremic syndrome **Definition:** A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia Signs and symptoms of HUS can include: • Bloody diarrhea • Decreased urination or blood in the urine • Abdominal pain, vomiting and occasionally fever • Pallor • Small, unexplained bruises or bleeding from the nose and mouth • Fatigue and irritability • Confusion or seizures • High blood pressure • Swelling of the face, hands, feet or entire body	
Diagnostic Workup: • History and PE (special consideration for new history of high risk drugs, HTN or cardiac causes) • CBC with indices • Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis	

- Serum creatinine
- ADAMTS13 (to rule out TTP)
- Homocystiene/MMA
- Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial)
- Evaluate reticulocyte count and MCV
- Evaluation of infectious cause including screening for viral EBV, CMV, HHV6
- Evaluation for nutritional causes of macrocytosis (B12 and folate)
- Pancreatic enzymes
- Evaluation for diarrheal causes, shiga toxin, Escherichia coli 0157, etc
- Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia
- Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus etc)
- Evaluation for concurrent confusion

Grading	**Management**
G1-2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia grade II	• Continue ICPi with close clinical follow-up and laboratory evaluation • Supportive care
G3: Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	• Permanently discontinue ICPi • Begin therapy with Eculizumab therapy 900mg weekly x 4 doses, 1200mg week 5, then 1200mg every two weeks. • Red blood transfusion according to existing guidelines
G4: Life-threatening consequences, (e.g., CNS thrombosis/embolism or renal failure)	

8.4 Aplastic Anemia
Definition: Condition in which the body stops producing enough new blood cells.

Diagnostic Workup:

- History and physical examination (close attention to medications, exposure to radiation, toxins, recent viral infections)
- CBC, smear, and reticulocyte count
- Viral studies including CMV, HHV6, EBV, parvovirus

- Nutritional assessments including b12, folate, iron, copper, ceruloplasmin, vitamin D
- Serum LDH, renal function
- W/u for infectious causes.
- Identify marrow hypo/aplasia
- BM biopsy and BM aspirate analysis
- Peripheral blood analysis including neutrophil count, proportion of GPI-negative cells by flow for PNH
- Flow cytometry to evaluate loss of GPI-anchored proteins
- Type and screen patient for transfusions and notify blood bank that all transfusions need to be irradiated and filtered

Grading	Management
G1: nonsevere: >0.5 polymorphonuclear cells (PMNs) $\times 10^9$/L hypocellular marrow, with marrow cellularity<25%, Peripheral platelet count >20,000, reticulocyte count >20,000	• Hold ICPi, provide growth factor support and close clinical follow-up and laboratory evaluation. • Supportive transfusions as per local guidelines
G2: severe: Hypocellular marrow <25% and tow of the following ANC <500, peripheral platelet <20,000 and Reticulocyte <20,000	• Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily • Administer ATG + cyclosporine. HLA typing and evaluation for bone marrow transplantation if patient is candidate. All blood products should be irradiated and filtered. • Supportive care with GCSF may be added in addition
G3-4: very severe: ANC<200, platelet count <20,000, reticulocyte count of <20,000, plus hypocellular marrow <25%.	• Hold ICPi and monitor weekly for improvement. If not resolved, discontinue treatment until AE has reverted to grade 1 • Hematology consult, growth factor support • Horse ATG plus cyclosporine • If no response, repeat immunosuppression with Rabbit ATG plus cyclosporine, cyclophosphamide • For refractory patients consider eltrombopag plus supportive care

<table>
<tr><td colspan="2">8.5 Lymphopenia
Definition: An abnormally low level of lymphocytes in peripheral blood (PB); for adults, counts of less than 1,500/mm^3</td></tr>
<tr><td colspan="2">Diagnostic Workup:
• History and physical exam (special attention for lymphocyte depleting therapy such as Fludarabine, ATG, steroids, cytotoxic chemotherapy, radiation exposure etc. well as history of autoimmune disease, family history of autoimmune disease)
• Evaluation of nutritional state as cause
• Spleen size
• CBC with differential, peripheral smear and reticulocyte counts
• CXR for evaluation of presence of thymoma
• Bacterial cultures and evaluation for infection (fungal, viral, bacterial specifically CMV/HIV</td></tr>
<tr><td>G1-2: 500-1000 PB lymphocyte count</td><td>• Continue ICPi</td></tr>
<tr><td>G3: 250-499 PB lymphocyte count</td><td>• Continue ICPi, checking CBC weekly for monitoring, initiation of CMV screening</td></tr>
<tr><td>G4: <250 PB lymphocyte count</td><td>• Consider holding ICPi
• Initiate Mycobacterium avium complex prophylaxis and Pneumocystis jirovecii prophylaxis, CMV screening. HIV/hepatitis screening if not already done.
• May consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis occur c/w lymphoproliferative disease occurs</td></tr>
<tr><td colspan="2">8.6 Immune thrombocytopenia (ITP)
Definition: an autoimmune disorder characterized by immunologic destruction of otherwise normal platelets</td></tr>
<tr><td colspan="2">Diagnostic Workup:
• Initiate Mycobacterium avium complex prophylaxis and Pneumocystis jirovecii prophylaxis, CMV screening. HIV/Hepatitis screening if not already done.
• History and physical examination (special attention for lymphocyte depleting therapy such as Fludarabine, ATG, steroids, cytotoxic therapy)
• FH of autoimmunity or personal history of autoimmune disease
• History of viral illness</td></tr>
</table>

• CBC • Peripheral blood smear, reticulocyte count • Bone marrow evaluation only if abnormalities in the above testing results and further investigation is necessary for a diagnosis • Patients with newly diagnosed ITP should undergo testing for HIV , HCV, HBV and H. pylori • Direct antigen test should be checked to rule out concurrent Evan's syndrome • Nutritional evaluation • BM evaluation if other cell lines affected and concern for aplastic anemia	
Grading	**Management**
G1: Platelet count <100/μL	• Continue ICPi with close clinical follow-up and laboratory evaluation
G2: Platelet count <75/μL	• Hold ICPi, but monitor for improvement. If not resolved, interrupt treatment until AE has reverted to Grade 1 • Administer prednisone 1 mg/kg per day (dosage range, 0.5–2 mg/kg per day) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose • IVIG may be used in conjunction with corticosteroids if a more rapid increase in platelet count is required.
G3: Platelet count <50/μL	• Hold ICPi, but monitor for improvement. If not resolved, interrupt treatment until AE has reverted to Grade 1 • Hematology consult
G4: Platelet count <25/μL	• Prednisone corticosteroids 1-2 mg/kg/day (oral or IV depending on symptoms) • If worsening or no improvement, 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue treatment • IVIG be used with corticosteroids when a more rapid increase in platelet count is required • If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary • If previous treatment with corticosteroids and/or, IVIG, has been unsuccessful, subsequent treatment may include

	rituximab, thrombopoietin receptor agonists, or more potent immunosuppression (*From American Society of Hematology guideline on immune thrombocytopenia[13] – consult for further details)*
8.7 Acquired Hemophilia **Definition:** disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors,	
Diagnostic Workup: • If previous treatment with corticosteroids and/or, IVIG, has been unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more potent immunosuppression • Full blood count to assess platelet number, fibrinogen, PT, PTT, INR. The typical finding in patients with AHA is a prolonged aPTT with a normal prothrombin time (PT). • MRI, CT, and ultrasonography may be indicated to localize, quantify, and serially monitor the location and response of bleeding. • Medication review to assess for alternative causes • Determination of Bethesda unit level of inhibitor	
Grading	**Management**
G1: Mild: 5-40% of normal factor activity in blood; 0.05-0.4 IU/ml of whole blood	• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits • Administer 0.5 to 1 mg/kg/day prednisone • Transfusion support as required • Treatment of bleeding disorders with hematology consult
G2: Moderate: 1-5% of normal factor activity in blood; 0.01-0.05 IU/ml of whole blood	• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits • Hematology consult • Administration of factor replacement (choice based on BU of titer) • Administer 1 mg/kg/day prednisone ± rituximab (dose 375mg/m2 weekly x 4 weeks) and/or cyclophosphamide (dose 1-2mg/kg/day). Choice of rituximab vs cyclophosphamide is patient specific and should be done with assistance of hematology consult. Prednisone, rituximab

	and cyclophosphamide should be given for at least 5 weeks. • Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor
G3-4: Severe: <1% of normal factor activity in blood; < 0.01 IU/ml of whole blood	• Permanently discontinue ICPi • Admit patient • Hematology consult • Administration of factor replacement, choice based on BU level of inhibitor. • Bypassing agents may be used (Factor VII FEIBA). Caution should be taken in elderly and those with CAD • Prednisone corticosteroids 1-2 mg/kg/day (oral or IV depending on symptoms)± rituximab (dose 375mg/m2 weekly x 4 weeks) and/or cyclophosphamide (dose 1-2mg/kg/day). • Transfusion support as required for bleeding • If worsening or no improvement add, cyclosporine, or immunosuppression/immunoadsorption
Additional Considerations: • AHA requires specialist clinical and laboratory expertise. Consult and/or transfer to a specialist center is often appropriate. If consultation with or transfer to a hemophilia center is not immediately possible, then investigation and treatment should be initiated while a liaison is being established.[14]	
9.0 CARDIOVASCULAR TOXICITY	
9.1 Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis **Definition:** *Signs and symptoms may include*: chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, fatigue	
Diagnostic Workup: At baseline: • Electrocardiogram • Consider Troponin, especially in patient treated with combination immune therapies Upon signs/symptoms (Consider cardiology consult)	

<table>
<tr><td colspan="2">
• Electrocardiogram
• Troponin
• BNP
• Echocardiogram
• Chest X-ray
Additional testing to be guided by cardiology and may include:
• Stress test
• Cardiac catherization
Cardiac MRI
</td></tr>
<tr><th>Grading</th><th>Management</th></tr>
<tr><td>G1: Abnormal cardiac biomarker testing, including abnormal ECG

G2: Abnormal screening tests with mild symptoms

G3: Moderately abnormal testing or symptoms with mild activity

G4: Moderate to severe decompensation, intravenous medication or intervention required, life threatening conditions</td><td>All grades warrant workup and intervention given potential for cardiac compromise
Please consider the following:
• Hold ICPi and permanently discontinue after G1
• High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms).
• Admit patient, cardiology consultation
• Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology
• Immediate transfer to a coronary care unit should be considered for patients with elevated troponin or conduction abnormalities.
• In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1g every day) and the addition of either mycophenolate, infliximab, or anti-thymocyte globulin</td></tr>
<tr><td colspan="2">Qualifying Statement: Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications. Holding checkpoint inhibitor therapy is recommended for all grades of complications. The appropriateness of rechallenging remains unknown. Note that infliximab has been associated with heart failure and is contraindicated at high doses in patients with moderate-severe heart failure. [15]</td></tr>
</table>

9.2 Venous thromboembolism
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.
Clinical signs and symptoms are variable and may include pain, swelling, increased skin vein visibility, erythema, and cyanosis accompanied by unexplained fever for DVT and dyspnea, pleuritic pain, cough, wheezing or hemoptysis for PE

Diagnostic Workup:
Evaluation of signs and symptoms of PE or DVT may include:

- Admit patient, cardiology consultation
- Clinical prediction rule to stratify patients with suspected VTE
- Venous US for suspected DVT
- CTPA for suspected PE
- Can also consider D-dimer for low risk patients based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler not available or appropriate
- V/Q scan is also an option when CTPA is not appropriate
- Consider other testing, including ECG, chest radiography, BNP and troponin levels, and ABG

Grading	Management
G1: Venous thrombosis (e.g., superficial thrombosis)	• Continue ICPi • Warm compress • Clinical surveillance
G2: Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	• Continue ICPi • Management according to CHEST, ACC and/or AHA guidelines and consider consult from cardiology or other relevant specialties • LMWH is suggested over VKA, dabigatran, rivaroxaban apixaban, or edoxaban for initial and long-term treatment • IV heparin is an acceptable alternative for initial use and oral anticoagulants are acceptable for the long term
G3: Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	
G4: Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency);	• Permanently discontinue ICPi • Admit patient and management according to CHEST, ACC and/or AHA guidelines and with guidance from cardiology • Respiratory and hemodynamic support

hemodynamic or neurologic instability; urgent intervention indicated	• LMWH is suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment • IV heparin is an acceptable alternative for initial use and oral anticoagulants are acceptable for the long term • Further clinical management as indicated based on symptoms

Additional Considerations:

- While it may be impossible to determine the etiology of thromboembolic disease in patients with advanced cancer and the role, if any, that ICPi treatment plays, it is reasonable to remove the potential inciting agents given the severity and life-threatening potential of grade 4 complications. Clinicians are to use clinical judgement and take into account the risks and benefits when deciding whether to discontinue ICPi treatment.
- Anticoagulant therapy duration should continue for a minimum of 9-12 months to indefinitely in the setting of active cancer unless patient is asymptomatic, doing well, or in remission.[16,17]

10.0 OCULAR TOXICITY

Counsel all patients to inform their healthcare provider immediately if they experience any of the following ocular symptoms:

- Blurred vision
- Change in color vision
- Photophobia
- Distortion
- Scotomas
- Visual Field changes
- Double vision
- Tenderness
- Pain with eye movement
- Eyelid swelling
- Proptosis

Evaluation, under the guidance of ophthalmology:

- Respiratory and hemodynamic support
- Check vision in each eye separately
- Color vision
- Red reflex

- Pupil size, shape and reactivity
- Fundoscopic examination
- Inspection of anterior part of eye with penlight

Prior Conditions

- Inspection of anterior part of eye with penlight
- Exclude patients with history of active uveitis
- History of recurrent uveitis requiring systemic immunosuppression or continuous local therapy

Additional Considerations:

- Ocular irAEs are many times seen in the context of other organ irAEs
- High level of clinical suspicion as symptoms may not always be associated with severity
- Best to treat after ophthalmologist eye examination

10.1 Uveitis/Iritis **Definition:** Inflammation of the middle layer of the eye	
Diagnostic Workup: As per 10.0	
Grading	**Management**
G1: Asymptomatic	• Continue ICPi • Refer to ophthalmology within 1 week • Artificial Tears
G2: Medical Intervention required, anterior uveitis	• Hold ICPi temporarily until after ophthalmology consult • Urgent Ophthalmology referral • Topical corticosteroids, cycloplegic agents, systemic corticosteroids • May resume ICPi treatment once off systemic steroids which are purely indicated for ocular side effect or once corticosteroids for other concurrent systemic irAE are reduced to ≤10mg. Continued topical/ocular steroids are permitted when resuming therapy to manage and minimize local toxicity • Retreat after return to ≤ G1
G3: Posterior or pan-uveitis	• Permanently discontinue ICPi

	• Urgent ophthalmology referral. • Systemic corticosteroids and intravitreal/periocular/topical corticosteroids
G4: 20/200 or worse	• Permanently discontinue ICPi • Emergent ophthalmology referral. • Systemic corticosteroids - IV prednisone 1-2mg/kg or methylprednisolone 0.8-1.6mg/kg and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion
Additional Considerations: Consider use of infliximab or other TNFa blockers in cases that are severe and refractory to standard treatment. [18,19]	
10.2 Episcleritis **Definition:** Inflammatory condition affecting the episcleral tissue between the conjunctiva and the sclera that occurs in the absence of an infection	
Diagnostic Workup: As per 10.0	
Grading	**Management**
G1: Asymptomatic	• Continue ICPi • Refer to ophthalmology within 1 week • Artificial Tears
G2: vision 20/40 or better	• Hold ICPi therapy temporarily until after ophthalmology consult • Urgent ophthalmology referral • Topical corticosteroids, cycloplegic agents, systemic corticosteroids
G3: Symptomatic and vision worse than 2/40	• Permanently discontinue ICPi • Urgent ophthalmology referral. • Systemic corticosteroids and topical corticosteroids with cycloplegic agents
G4: 20/200 or worse	• Permanently discontinue ICPi • Emergent ophthalmology referral. • Systemic corticosteroids and topical corticosteroids with cycloplegic agents
Additional Considerations: Consider use of infliximab or other TNFa blockers in cases that	

are severe and refractory to standard treatment. [18,19]
10.3 Blepharitis **Definition:** Inflammation of the eyelid that affects the eyelashes or tear production
Diagnostic Workup: As per 10.0

Grading	Management
No formal grading system	• Warm compresses and lubrication drops • Continue therapy unless persistent and serious

MODEL INFORMED CONSENT FORM

VERSION LOG

Version	Date	Reason for Change
1.0	*09 Mar 2018*	*Not applicable*
2.0	*04 Apr 2018*	*Update of the information about the optional exploratory biomarker assay*
3.0	*18 Sep 2018*	*Update as per protocol V2.0 and IB V3.0*
4.0	12Jun2019	*Update as per protocol V3.0 and IB V4.0*
5.0	*12Jun2020*	*Update as per protocol V4.1 and IB V5.0*
6.0	*18Aug2020*	*Update as per protocol V5.0*

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CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

Title of Study	**A PHASE III, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER, DOUBLE-BLIND STUDY COMPARING TORIPALIMAB INJECTION (JS001) COMBINED WITH CHEMOTHERAPY VERSUS PLACEBO COMBINED WITH CHEMOTHERAPY FOR RECURRENT OR METASTATIC NASOPHARYNGEAL CANCER**
Protocol Number	**JS001-015-III-NPC**
Aligned with protocol version and date	**5.0/18Aug 2020**
Sponsor	**Shanghai Junshi Biosciences Co., Ltd.**
Investigator	
Patient	
Date of Document:	**18Aug2020**

1 WHY HAVE I BEEN GIVEN THIS FORM?

You are being invited to take part in a clinical research study of an investigational drug, Toripalimab injection (JS001), to treat recurrent or metastatic nasopharyngeal cancer. Toripalimab injection was approved by Chinese National Medical Products Administration on 17 Dec 2018 for the treatment of non-resectable or metastatic melanoma that has failed systemic treatment.

Before you decide if you want to take part in this study, it is important for you to understand

- Why the study is being done,
- How your information will be used,
- What the study will involve, and
- The possible benefits, risks and discomforts for you when you take part.

Please take time to read the following information carefully. Some terms may be new to you. If there is anything you do not understand or if you would like more information, please ask the study doctor or study staff. You may also discuss the study with family

members, friends, and your own doctor if you wish. If you decide that you want to take part in this study, you will be asked to sign the consent statement at the end of this informed consent form (you will be given a copy of this to take home with you). You must not take part in any study procedures until you have read and signed this form.

2 DO I HAVE TO TAKE PART?

It is up to you to decide if you want to take part. You are free to choose not to take part. Even if you choose not to take part in this study, you will not be disadvantaged in any way, including all medical treatment and care you have the right to receive. If you choose to take part, you may change your mind and choose to leave the study at any time for any reason. You will not need to explain your reasons for leaving the study. If you leave the study, you will not bear any penalty or loss of benefits regarding your future care.

The study doctor can withdraw you from the study at any time if he or she feels it is in your best interest or if you cannot comply with study requirements.

Your participation in the study may also be stopped by the Sponsor or by the regulatory authorities at any time. Further, your participation may also be stopped by an independent ethics committee such as the Institutional Review Board (IRB) or Institutional Ethics Committee (IEC) at any time without your consent. These committees review study safety and ethics to make sure that patients' rights are not violated. The reason(s) for stopping the study will be explained to you, and you will be given advice about continued care for your condition, if this is appropriate. In addition, the Sponsor has the right to stop the study for medical or business reasons. If this happens, all patients taking part in the study will be withdrawn.

If you leave (or withdraw from) the study, you will be asked to go through study withdrawal procedures detailed in Section 6 and information about you will be handled as detailed in Section 14.

3 WHO IS THE SPONSOR OF THIS STUDY?

This clinical research study is being sponsored by Shanghai Junshi Biosciences Co., Ltd. (hereafter referred to as the Sponsor).

4 WHAT IS THE STUDY ABOUT?

Toripalimab injection (JS001, hereafter referred to as the Study Drug) is a monoclonal antibody acting on programmed cell death-1 (PD-1). Antibodies are a common type of proteins, through which the immune system finds and destroys bacteria, viruses and other foreign molecules. Antibodies can also be produced in the laboratory, and used for the

treatment of patients. Currently, several antibodies have been approved for the treatment of cancer and other diseases.

PD-1 is a protein present on the surface of immune cells. After binding to its ligand, PD-1 inhibits immune cells from killing cancer cells. The Study Drug acts on PD-1, thereby stopping it from inhibiting immune cells, so that immune cells can attack cancer cells.

In an initial dose escalation Phase I study in patients with advanced solid tumors (melanoma, urothelial carcinoma, and renal cell carcinoma), the Study Drug showed a good safety profile, with no dose limiting toxicity (DLT) observed and no maximum tolerated dose (MTD) reached. Treatment-related side effects were similar to those from approved drugs of the same class. The most common treatment-related adverse events (AEs) were mild or moderate in intensity and the emergence of AEs was not dose related. The Study Drug has shown promising effect on certain kinds of tumors, especially in previously under-evaluated acral and mucosal melanomas. In addition, in an ongoing Phase Ib/II study, patients with advanced gastric adenocarcinoma, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, and head and neck squamous cell carcinoma who had failed at least one previous line standard anti-tumor treatment are being treated with the study drug on its own (monotherapy). Results so far from this study indicate that the monotherapy with study drug is effective against tumors and has manageable side effects (more than half of the AEs reported so far were mild or moderate in intensity).

This study is to find out if the Study Drug combined with chemotherapy is more effective in the treatment of recurrent or metastatic nasopharyngeal cancer than placebo combined with chemotherapy. The study will recruit approximately 280 subjects at about 40 study centers in China mainland, Taiwan, and Singapore. Participants with nasopharyngeal cancer who qualify for the study and agree to take part will be allocated into one of the 2 groups, either to receive the Study Drug plus gemcitabine and cisplatin, or placebo plus gemcitabine and cisplatin. The placebo is a medicine that looks like the Study Drug but does not contain the “active” ingredients.

The group that you will be in is decided by chance, like tossing a coin or drawing names out of a hat. About 50% of patients will receive the Study Drug plus gemcitabine and cisplatin and about 50% will receive placebo plus gemcitabine and cisplatin. To make the comparison between Study Drug and placebo as fair as possible, this study is “double blinded.” This means that neither you nor the study doctor will know which kind of treatment you are receiving. The study doctor will be able to find out which treatment you are receiving if necessary, to treat any side effects that you may have.

This study consists of 4 periods: a screening period, a during-chemotherapy period, a post-chemotherapy period, and a survival follow-up period. The screening period takes up to 28 days. The during-chemotherapy period starts from the first dosing day of the Study Drug, and will continue until progressive disease, excessive toxicity, noncompliance,

withdrawal of consent, or a maximum of 6 cycles (every 3 weeks is referred to as a "Cycle"), whichever occurs first. The post chemotherapy period follows the during-chemotherapy period, and will continue until excessive toxicity, progressive disease, withdrawal of consent or study doctor's judgement, or a maximum of 2 years whichever comes first.

At the end of the study and if you were randomized to the JS001 arm during the study, your study doctor and the Sponsor will evaluate if you are eligible to continue the treatment with the Study Drug（JS001） after completing the study based on certain conditions (your health conditions, the efficacy and safety of the Study Drug, etc). If you are eligible, the Sponsor will continue to provide the Study Drug （JS001）free of charge to you in accordance with local regulations. Patients who were randomized to the placebo arm are not permitted to cross over to receive Study Drug（JS001）.

5 WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to compare the effects, good or bad, of the Study Drug plus gemcitabine and cisplatin versus placebo plus gemcitabine and cisplatin on you and your disease, to find out which is better. In this study, you will get either Study Drug plus gemcitabine and cisplatin or placebo plus gemcitabine and cisplatin.

You will also be asked if you are willing to take part in an optional biomarker research involving analysis of the optional tumor tissue samples collected when your cancer appeared to have worsened. This optional biomarker research is to evaluate certain biomarkers (some molecules and cells in your body) which could help doctors to better understand your disease and/or your response to the Study Drug. Such analysis may include analysis of the biological feature of your tumor tissue. You will be asked to sign a separate consent form if you agree to take part in the optional biomarker research.

You will also be asked if you are willing to donate any remaining blood samples for the exploratory biomarker assay in case there are remaining blood samples from the mandatory analysis. You should read the following sections carefully to see how your remaining blood samples will be tested and state if you are willing to donate your remaining blood samples by checking the corresponding boxes on the signature page of this informed consent form (See Section 16).

6 WHAT WILL HAPPEN TO ME DURING THE STUDY?

No study-related procedures may be conducted before signing of this informed consent.

Study Medication

The Study Drug or placebo will be administered once every cycle (every 3 weeks) throughout the during-chemotherapy period and post-chemotherapy period. The Study

Drug will be administered in one of your veins (intravenously [IV]) in 100 mL 0.9% NaCl infusion bags at the dose of 240 mg on Day 1 of each cycle in the study center. Placebo will be given in the same way as the Study Drug in order to keep blind. The treatment (infusion) of the study drug or placebo will be administered about 60 minutes during the first 2 cycles. If no clinically significant infusion reaction is observed during or after the first 2 cycles, the Study Drug will be administered as a 30-minute IV infusion afterward. After each infusion, you will be monitored for a period of 60 minutes (only required in the first 2 cycles).

Chemotherapy will be given only in the during-chemotherapy period (up to 6 cycles). Gemcitabine will be given IV over 30 minutes on Day 1 and Day 8 of each cycle, and cisplatin will be given IV over 4 hours on Day 1 of each cycle.

Study Visits

Screening Visit (From 1 Day up to 28 Days before Entering the During Chemotherapy Period)

At screening visit, you will first sign the informed consent form. After that, the study personnel will perform the following examinations/procedures for you to see if you meet all eligibility criteria.

- Ask your gender, age, race/ethnicity, and other basic information, and collect your medical history information, including your diseases, surgeries, cancer history, smoking history, childbearing history, drug/alcohol abuse, and treatment information.
- You will be assessed for vital signs, including body temperature, pulse, blood pressure, and respiratory rate; you will also have a physical examination, including weight and height measurement.
- The study doctor will assess your general well-being and ability to perform daily activities (performance status).
- 12-lead electrocardiogram (ECG): This is a painless, non-invasive test that shows how your heart works (takes a picture of the electrical activity of your heart). To have the ECG, you will lie on a bed/couch for several minutes with sensors called electrodes, which are sticky patches, taped to your arms, legs, and chest.
- Echocardiogram: An echocardiogram is a type of ultrasound test that uses high pitched sound waves that are sent through a device called a transducer. The device picks up echoes of the sound waves as they bounce off the different parts of your heart. These echoes are turned into moving pictures of your heart that can be seen on a video screen. It helps to evaluate the size, shape, and function of the heart.

- Blood samples will be taken for laboratory tests, including CBC, blood chemistry, thyroid function, and coagulation parameters. You will also have blood taken to test for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). HBV DNA and/or HCV RNA will be measured if your study doctor thinks it necessary, to find out the status of the hepatitis virus infection. If you are a woman who is able to become pregnant/have children, a blood sample will be collected for a pregnancy test. If you are pregnant, you cannot take part in this study. The volume of the blood samples is around 21-25 mL.
- A urine sample of 10 mL will be collected during screening for urinary routine analysis.
- You will be asked about any new disease or discomfort you have experienced, as well as any medications you have used.
- Tumor assessment: You will have computed tomography (CT) scans (with oral/IV contrast unless contraindicated) or magnetic resonance imaging (MRI) of the nasopharynx, neck, chest, and abdomen. A CT scan is an X-ray that is transmitted onto a computer that gives your doctor clearer pictures of the inside of your body. A contrast medium is like a dye that will spread through your body and will help give clearer images. An MRI scan is an imaging procedure that uses radiowaves and a magnetic field to take pictures of the inside of your body. During the MRI scan, you may be asked to lie down on your back on a table and you will need to remain still until the pictures have been taken. A CT (with contrast) or an MRI scan of the brain is required to confirm or rule out the spread of cancer cell to the brain. Bone scans or other assessments to measure your disease should also be performed if your study doctor thinks them necessary.
- Tumor tissue sampling: if you have had a tumor biopsy/tumor operation, the study doctor will request the original sample from the original biopsy from the hospital where the biopsy was taken. If there is no archived sample, you will be required to have a biopsy sample from tumor tissue collected by your study doctor before or within 4 weeks after entering the study. In addition, to take part in this study, you must allow the study center to obtain the original sample, and allow the study doctor to send samples to the laboratory for research test. The laboratory will test your tumor samples to determine whether there are some features of your tumors, help scientists better understand the nasopharyngeal cancer, and help scientists understand why the study drug is effective or ineffective to your specific cancer type.The

remaining tumor tissue samples will be returned to the study center if there are any remains after completing the required testing.

If you have tests or examinations for ECG, echocardiogram, physical examination, thyroid function, HBV, HCV, HIV, EBV or tumor assessment performed before the Screening Visit but within 28 days prior to C1D1, you do not need to repeat them at the Screening Visit.

After screening, if you qualify for the study, you will enter the during-chemotherapy period. Your study doctor will carefully arrange your hospitalization and follow-up schedule. The following processes need your cooperation.

During-Chemotherapy Period (starting from the first dose of the Study Drug to a maximum of 6 cycles)

You will return to the study center for visits on Day 1 and Day 8 of each cycle in this period. During the visits on Day 1 of each cycle, you need to have assessments/procedures as follows:

- You will be asked to complete questionnaires about your life and health. The information collected from these questionnaires is valuable and important to us, and will allow analyses on your medical measurements and quality of life.
- You will be assessed for vital signs, including body temperature, pulse, blood pressure, and respiratory rate.
- The study doctor will assess your performance status.
- You will have a limited physical examination, including body weight measurement (your weight will not be measured on C1D1).
- 12-lead ECG and echocardiogram will be performed if your study doctor thinks it necessary.
- A urine sample of 10 mL will be collected for urinary routine analysis (not on C1D1). If you are a woman who is able to become pregnant/have children, a urine sample of 5 mL will also be collected for a pregnancy test (not on C1D1). Samples must be collected within 3 days prior to the treatment(except for C1D1).
- Blood samples will be taken within 3 days (except for C1D1) prior to the treatment for laboratory tests, including CBC, blood chemistry, and thyroid function (not on C1D1). If your urine pregnancy test is positive, a blood sample will be collected for a further pregnancy test (not on C1D1). Blood coagulation test will be performed if your study doctor thinks it necessary (not on C1D1). The volume of the blood samples is around 12-16 mL at each visit.

- Blood samples of 3 mL will be taken for EBV test before the treatment on Day 1 of Cycle 1 (C1D1) , Day 1 of Cycle 3 (C3D1) and Day 1 of Cycle 5 (C5D1).
- Blood samples will be taken for anti-drug antibodies (ADA) and JS001 concentration assessment before the treatment on C1D1, Day 1 of Cycle 5(C5D1) . It helps to investigate if your body produces any response against the Study Drug. The volume of the blood samples is around 3 mL.
- Blood samples of 10 mL will be taken for biomarker assessment before the treatment on C1D1, C3D1, and C5D1.
- You will have CT scans (with oral/IV contrast unless contraindicated) or MRI every 6 weeks during-chemotherapy period, that would happen around on C3D1 and C5D1. You may have additional CT scans if you study doctor thinks it necessary.
- You will be asked about any new disease or discomfort you have experienced, as well as any medications you have used since last visit.
- The Study Drug or placebo will be given via IV infusion. Gemcitabine and cisplatin will be given via IV infusion on the same day.

During the visits on Day 8 of each cycle in this period, you need to have assessments/procedures as follows:

- The study doctor will assess your performance status.
- You will be assessed for vital signs, including body temperature, pulse, blood pressure, and respiratory rate.
- 12-lead ECG and echocardiogram will be performed if your study doctor thinks it necessary.
- Blood samples will be taken within 3 days before the treatment for laboratory tests including CBC and blood chemistry. Blood coagulation test will be performed if your study doctor thinks it necessary. The volume of the blood samples will be around 7-9 mL at each visit.
- You will be asked about any new disease or discomfort you have experienced, as well as any medications you have used since last visit.
- Gemcitabine will be given via IV infusion.

Post-Chemotherapy Period (starting from Cycle 7 to a maximum of 2 years)

At subsequent treatment cycles, you will return to the study center for visits on Day 1 of each cycle, and you need to have assessments/procedures as follows:

- You will be asked to complete questionnaires about your life and health.

- You will be assessed for vital signs, including body temperature, pulse, blood pressure, and respiratory rate.
- You will have a limited physical examination.
- The study doctor will assess your performance status.
- 12-lead ECG and echocardiogram will be performed if your study doctor thinks it necessary.
- A urine sample of 10 mL will be collected for urinary routine analysis. If you are a woman who is able to become pregnant/have children, a urine sample of 5 mL will also be collected for a pregnancy test. Samples must be collected within 3 days prior to the treatment.
- Blood samples will be taken within 3 days prior to the treatment for laboratory tests, including CBC, blood chemistry, and thyroid function. Blood coagulation test will be performed if your study doctor thinks it necessary. If your urine pregnancy test is positive, a blood sample will be collected for a further pregnancy test. The volume of the blood samples is around 12-16 mL at each visit.
- Blood samples of 3 mL will be taken for EBV test before the treatment every 2 cycles for 12 months following C1D1, and then every 3 cycles thereafter until initial disease progression.
- Blood samples of 3 mL will be taken for ADA and JS001 concentration assessment before the treatment every 4 cycles for the first year following C1D1, and then every 8 cycles thereafter until discontinuation of study drug.
- Blood samples of 10 mL will be taken for biomarker assessment before the treatment every 2 cycles for the first year following C1D1, and then every 6 cycles thereafter until initial disease progression.
- You will have CT scans (with oral/IV contrast unless contraindicated) or MRI every 6 weeks (approximately every 2 cycles) for 12 months following C1D1, and then every 9 weeks (approximately every 3 cycles) thereafter. You may have additional CT scans if your study doctor thinks it necessary.
- You will be asked about any new disease or discomfort you have experienced, as well as any medications you have used since last visit.
- The Study Drug or placebo will be given via IV infusion.

Treatment Discontinuation/Completion Visit

At 30 days after the last dose of the Study Drug, you will attend a treatment discontinuation/completion visit and have assessments/procedures including:

- You will be assessed for vital signs, including body temperature, pulse, blood pressure, and respiratory rate.
- You will have a limited physical examination, including body weight measurement.
- The study doctor will assess your performance status.
- 12-lead ECG and echocardiogram will be performed if your study doctor thinks it necessary.
- A urine sample of 10 mL will be collected for urinary routine analysis. If you are a woman who is able to become pregnant/have children, a urine sample of 5 mL will also be collected for a pregnancy test.
- Blood samples will be taken for laboratory tests, including CBC, blood chemistry, and thyroid function. Blood coagulation test will be performed if your study doctor thinks it necessary. If your urine pregnancy test is positive, a blood sample will be collected for a further pregnancy test. The volume of the blood samples is around 12-16 mL.
- Blood samples of 3 mL will be taken for EBV assessment at the time of initial disease progression.
- Blood samples of 3 mL will be taken for ADA and JS001 concentration assessment at the time of study drug discontinuation.
- Blood samples of 10 mL will be taken for biomarker assessment at the time of initial disease progression.
- You will be asked about any new disease or discomfort you have experienced, as well as any medications you have used since last visit.

Survival Follow-Up Period

During this period, you will have a visit every 3 months after treatment discontinuation. Required follow-up information will be collected via telephone calls and/or study center visits. You will be asked about any new disease or discomfort you have experienced since your last call/visit.

If you discontinued from the study treatment before disease progression and did not start any new anti-cancer therapy, you are advised to continue the CT scans or MRI for following the disease progression per the frequency (every 6 weeks for 1 year following C1D1, and then every 9 weeks thereafter) of the study.

Unplanned Visit

If your study doctor believes that you should have extra visit(s) for your safety, e.g., if you have a new symptom or side effect, you may be asked to come for an extra visit. The procedures you may have include but not limited to:

- You will be assessed for vital signs, including body temperature, pulse, blood pressure, and respiratory rate.
- The study doctor will assess your performance status.
- 12-lead ECG and echocardiogram will be performed if your study doctor thinks it necessary.
- You will be asked about any new disease or discomfort you have experienced, as well as any medications you have used since last visit.
- You will have other assessments if your study doctor thinks them necessary.

Initial Radiographic Disease Progression

While receiving treatment in the study, your study doctor may find that your tumor has started to grow again. It has been shown in other similar investigational studies that in a small number of study participants, there is evidence that although the cancer has appeared to have worsened (that is, the tumors appear to have got bigger on the scan), the study drug is actually working. This is called “pseudo-progression”, which happens because immune cells activated by the study drug are starting to infiltrate the cancer and attack the cancer cells. This makes the tumor more swollen and so it appears larger on the scan.

If the Sponsor medical monitor or designee and your study doctor evaluate that you will benefit from continuing the treatment and certain criteria are fully met, you will have the option to continue Study Drug (Toripalimab or placebo) treatment. In this case, you will continue to have all the same visits and assessments as detailed above. However, you must permanently discontinue Study Drug treatment when you experience second progression.

Continuing study drug treatment after tumor progression is not a common standard procedure; you can also choose other alternative treatments, such as other approved drugs for the treatment of cancer or other clinical studies. You should discuss treatment options with your study doctor. If after discussion, you, your study doctor, and Sponsor medical monitor consider that continuing Study Drug treatment is the best choice, then you need to sign the signature page "Treatment Through Progression Consent Form", to show that you agree to continue Study Drug/placebo treatment and you are willing to undertake subsequent visits in accordance with the above procedure.

Optional Tumor Biopsy

The optional tumor biopsy is performed for the optional biomarker research to find out why the tumor grows bigger (pseudo-progression, tumor immune infiltration, or true disease progression). The tumor sample will be collected within 40 days of radiographic progression or before start of the next anti-cancer treatment, whichever is sooner. If you are willing to have the optional tumor biopsy for the optional biomarker research, you need to sign a separate form "Biomarker Research Informed Consent Form".

Optional Exploratory Biomarker Assay

If there are remaining blood samples from the mandatory analysis, and you agree to donate these remaining blood samples for the exploratory biomarker assay, tests of biomarkers in your remaining blood samples (plasma, serum, and whole blood) will be done. The biomarkers to be tested may include but may not be limited to DNA, RNA, and other molecules. Cells in your body contain a type of molecule called deoxyribonucleic acid, or DNA for short. DNA is what your genes are made of. Genes are inherited and direct growth, development, and how the body functions. There are many differences, or variations, in DNA from one person to another. These variations may affect a person's chance of suffering from a particular disease or the way a person responds to a particular drug. A gene is used to make RNA, which provides instructions for cell function and helps determine the characteristics of people. It is up to you whether to donate your remaining blood samples or not. You may refuse to donate the remaining blood samples at any time without penalty or loss of benefits to which you are otherwise entitled. You will receive the same treatment and care in the study whether or not you agree to donate the remaining blood samples for the exploratory biomarker assay. You should be aware that the Sponsor might not conduct all exploratory biomarker assays immediately and that your samples may be studied at any time before they are destroyed. If you are willing to donate your remaining blood samples, you should check the corresponding boxes on the signature page of this form at the time of informed consent.

Blood Tests

All your test results are private and will be made known only as required by law.

Blood and urine samples will be taken for laboratory tests. Blood volumes for each test are listed in *Table 1*~~*Table 1Table 1*~~. The tests that will be done will include standard tests of your general health, tests of viral infections, tests of biomarkers, and a test of the drug antibody in your blood. If you are a woman who is able to become pregnant/have children, there will also be a blood pregnancy test at screening visit.

Table 1: Blood Volumes

Assessment	***Visit***				
	Screening	*During Chemotherapy Period (Day 1 of each cycle)*	*During Chemotherapy Period (Day 8 of each cycle)*	*Post Chemotherapy Period (Day 1 of each cycle)*	*Treatment Discontinuation/Completion Visit*
CBC	*2 mL*	*2 mL, not on C1D1*	*2 mL*	*2 mL*	*2 mL*
Blood chemistry	*3-5 mL*	*3-5 mL, not on C1D1*	*3-5 mL*	*3-5 mL*	*3-5 mL*
Thyroid function	*3-5 mL*	*3-5 mL, not on C1D1*	*NA*	*3-5 mL*	*3-5 mL*
Coagulation parameters	*2 mL*	*2 mL, if needed, not on C1D1*	*2 mL, if needed*	*2 mL, if needed*	*2 mL, if needed*
Testing for viral infections such as HBV, HCV and HIV	*3 mL*	*NA*	*NA*	*NA*	*NA*
Testing for EBV	*NA*	*3 mL,C1D1, C3D1 and C5D1 only*	*NA*	*3 mL[a]*	*3ml[d]*
Testing for HBV DNA	*3 mL, if needed*	*NA*	*NA*	*NA*	*NA*
Testing for HCV RNA	*3 mL, if needed*	*NA*	*NA*	*NA*	*NA*
Blood pregnancy	*2 mL*	*2 mL, if needed, not on C1D1*	*NA*	*2 mL, if needed*	*2 mL, if needed*
Testing for ADA and JS001 concentration	*NA*	*3 mL, C1D1 and C5D1 only*	*NA*	*3 mL[b]*	*3 mL[e]*
Testing for biomarker assessment	*NA*	*10 mL, C1D1, C3D1, and C5D1 only*	*NA*	*10 mL[c]*	*10 mL[d]*

a: every 2 cycles for 12 months following C1D1, and then every 3 cycles thereafter

b: every 4 cycles for the first year following C1D1, and then every 8 cycles thereafter

c: every 2 cycles for the first year following C1D1, and then every 6 cycles thereafter

d:at the time of initial disease progression

e:at the time of study drug discontinuation

ADA=anti-drug antibodies; C=cycle; D=day; DNA=deoxyribonucleic acid; EBV=Epstein-Barr virus; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; NA=not applicable; RNA=ribonucleic acid

Your blood samples and tumor tissue samples collected in the main study will be stored by the Sponsor with similar samples from other patients at secure central laboratories and at the Sponsor's facilities, which have experience in storing and analysing such samples. These laboratories may be located outside of the countries in which the study is conducted.The remaining ADA、EBV and biomarker samples will be destroyed per the central labs' SOP before study completion if there are any remains after completing the study required testing.

7 WHAT WILL I HAVE TO DO DURING THE STUDY?

If you decide to take part in this study, during the study period your responsibility is to closely cooperate with the study doctor's work, and strictly abide by the following:

- You will be firstly asked to sign this consent form if you agree to take part in this study. If you take part in this study, you should follow the study procedures and go to all the study visits. You should report any changes to your well-being, including any side-effects, to the study doctor.
- You will be expected to attend all visits listed in the study schedule and any others that may be deemed necessary. Please inform the study doctor if you will not be able to go to a visit.
- You cannot take any other therapy intended for the treatment of cancer, no matter it is health authority approved or experimental. This includes but is not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy.
- You should not be taking the following medications:
    - Traditional herbal medicines.
    - Denosumab; if you are receiving denosumab before entering the study, you must be willing and eligible to receive a bisphosphonate instead, while on study.
    - Any live, attenuated vaccine (e.g., FluMist®) within 4 weeks before randomization or at any time during the study.

- In case that CT scans with contrast are contraindicated for you, steroids will not be allowed before the scan. Instead, MRIs with a non-contrast CT scan will be performed.
- Prophylactic granulocyte colony stimulating factor are not allowed before the first cycle. Thereafter, they must be administered according to your condition by your study doctor.

Tell the study doctor before you start a new medication.

- Highly effective birth control methods are required during the study and for at least 60 days following the last dose of the Study Drug. Birth control methods allowed in this study include double-barrier method and total abstinence. Double-barrier method, like condom with spermicidal jelly, foam, suppository, or film; or diaphragm with spermicide; or male condom and diaphragm, works by preventing the sperm from getting to and fertilizing the egg. Spermicide is medications placed in the vagina to kill sperm when they come in contact. Abstinence means abstaining from sexual intercourse/having sexual intercourse. You should discuss methods of effective birth control with your study doctor.
  - **For women:** women who may be able to have children must use a double-barrier method during the study and for at least 60 days following the last dose of the Study Drug. The same request is also applied to the female partners of male patients.
  - **For men:** male patients must use appropriate birth control methods (total abstinence or condom with spermicide) during the study and for at least 60 days after the last dose of the Study Drug.
- Strenuous exercise should be avoided up to 72 hours before planned study visits.

8 WHAT ARE THE POSSIBLE RISKS?

The risks of side effects, complications, and/or injuries are both predictable and unpredictable in all research studies. In rare cases, certain risks can lead to serious injury or even death. It is important to note that it is not possible to predict all the side effects that may occur when you are given the study drug. New side effects not described in this ICF may occur in this study. If you experience any discomfort or deterioration of health during the study period, please notify your study doctor immediately, who will make a medical judgment regarding your condition and give you appropriate management and treatment.

Treatment-related side effects have been observed in clinical trials with Toripalimab (JS001) monotherapy

The side effects of the Study Drug on humans are not yet fully known. As of 16 Dec 2019, the clinical database contained preliminary safety data from 985 patients who received JS001 across multiple tumor types.

Adverse reactions observed in subjects who received JS001 monotherapy in clinical trials are presented as below:

Very common: may affect more than 1 in 10 people (≥10%)

- Anemia(reduction of red blood cell number or hemoglobin level),
- Rash,
- Coughing,
- Pruritus (itching),
- Asthenia (weak),
- Fever,
- Decreased appetite,
- Hypothyroidism (a decreased release of the thyroid hormone, which may result in tiredness, sluggishness, feeling cold or weight gain),
- Musculoskeletal pain,
- Leukopenia(white blood count decreased),
- Hyperglycemia(high level of blood sugar),
- ALT increased(elevation of liver enzyme),
- AST increased(elevation of liver enzyme),
- Thyroid stimulating hormone increased,
- Proteinuria (presence of protein in the urine).

Common: may affect up to 1 in 10 people (≥1% and <10%)

- Platelet count decreased,
- Headache,
- Dizziness,
- Hyperthyroidism(an increased release of thyroid hormone that may result in intolerance of heat, weight loss, weakness, palpitations, anxiety, heart rhythm abnormalities or heart failure),
- Dyspnea (difficulty in breathing),

- Abdominal pain,
- Vomiting,
- Lung infection),
- Hepatic function abnormalities,
- Interstitial lung disease,
- Skin depigmentation (absence or loss of pigmentation in the skin),
- Upper respiratory tract infection,
- Urinary tract infection,
- Lymphocytopenia (lymphocyte count decreased),
- Neutropenia (neutrophil count decreased),
- Infusion-related reactions，
- Hyponatremia(low blood sodium),
- Hypokalemia(low blood potassium),
- Hypocalcemia (low blood calcium),
- Insomnia(trouble falling and/or staying asleep)，
- Peripheral neuropathy(damage to the nerves outside of the brain and spinal cord),
- Blurred vision,
- Tachycardia(abnormally fast heart rate),
- Hypertension(high blood pressure),
- Constipation(difficulty passing stools),
- Nausea,
- Diarrhoea(frequent loose, watery stools),
- Stomatitis (inflammation of oral cavity),
- Dermatitis (inflammation of skin),
- Influenza-like illness,
- Peripheral oedema(swelling of legs or hands),
- Chest pain,
- Alkaline phosphatase (ALP) increased(elevation of enzyme, related with liver and/or bone),
- Blood bilirubin increased(abnormal testing related with liver function),
- Blood creatinine increased(abnormal testing related with kidney function),

- Amylase increased(elevation of enzyme, related with pancreas),
- Lipase increased(elevation of enzyme, related with pancreas),
- Creatine phosphatase kinase (CPK) increased(elevation of enzyme, related with muscles).

Uncommon: may affect up to 1 in 100 people (≥0.1% and <1%)

- Pancreatitis (inflammation of the pancreas),
- Diabetes mellitus(increase in blood sugar),
- Adrenal insufficiency,
- Hypersensitivity,
- Thyroiditis(inflammation of the thyroid),
- Hypophysitis(inflammation of pituitary gland),
- Hypopituitarism(decreased function of pituitary),
- Hepatitis(inflammation of the liver),
- Liver injury,
- Dysgeusia(dysfunction of the taste),
- Uveitis(inflammation of the eyes),
- Xerophthalmia(abnormal dryness of the eyes),
- Pericardial effusion(accumulation of fluid around the heart),
- Myocarditis (inflammation of the heart muscles)
- Pleural effusion(accumulation of fluid inside the chest),
- Pleurisy(inflammation of the pleural),
- Gastritis(inflammation of the stomach),
- Enteritis(Inflammation of the intestine),
- Gastroenteritis (Inflammation of the stomach and intestine),
- Myositis(inflammation of the muscles),
- Arthritis(inflammation of the joints),
- Renal injury,
- Troponin increased(elevation of the blood protein related to heart muscles),
- Cortisol decreased(decreased hormone, related with the function of the endocrine glands located on the top of kidney).

Immune-related Side Effects for the Study Drug

Since JS001 is recombinant humanized monoclonal antibody, the use of such drugs may cause associated side effects including systemic anaphylaxis, infusion reactions, and immune-related side effects. Some immune-related side effects may also be delayed, in which discomfort or abnormalities in laboratory tests occur long after administration.

Systemic allergic reactions: it may cause the following symptoms: swelling of the face, lips, and throat, dyspnea, and urticaria or urticaria-like rash. If you experience any of these symptoms above, you should notify your study doctor immediately.

Infusion reactions: it may occur during or after infusion of the study drug. These reactions may include fever or chills, changes in blood pressure, or dyspnea (which may be a serious event).If you experience any of these symptoms above, please inform your study doctor immediately.

The following immune-related side effects were observed, and the incidence data were obtained from a summary of safety information of 741 patients receiving the recommended therapeutic dose of JS001 in 9 single-arm studies:

•Immune-related pneumonitis (non-infectious lung inflammation, 1.8%): symptoms include, but are not limited to, the onset of cough or worsening cough, shortness of breath, and possibly fever. If you experience any of the above symptoms, please inform your study doctor immediately.

• Immune-related hepatitis (6.3%): liver function laboratory indicators, such as transaminase and bilirubin (the results of blood tests), are abnormal. The clinical manifestations of hepatitis may be yellowing of the skin or the whites of the eyes, fatigue, nausea and vomiting, right epigastric pain, itchy skin, and more bleeding and abrasions than normal. The study doctor will regularly assess your liver function laboratory indicators, and if your indicators are above certain criteria, your study doctor may need to stop the study drug.

• Hypothyroidism (13.6%): symptoms occur when the thyroid produces fewer thyroid hormones than normal, resulting in excessively slow metabolism. Symptoms include, but are not limited to, fatigue, increased cold sensitivity, constipation, dry skin, unexplained weight gain, facial swelling, muscle weakness, decreased heart rate, hair loss, and impaired memory. The condition can be treated with replacement thyroid hormones.

• Hyperthyroidism (4.7%): symptoms are due to excessive production of thyroid hormones by the thyroid gland. Symptoms include anxiety or nervousness, weight loss, increased and loose bowel movements, difficulty breathing, increased heat sensitivity, and possible heart palpitations. Depending on the severity of the symptoms, treatment may include monitoring the symptoms only, treating the symptoms and/or administering medication to block thyroid hormones.

• Immune-related diarrhea and colitis (0.9%): presenting with abdominal pain, diarrhea (loose bowels), possibly accompanied by fever.

• Immune-related skin toxicity (8.1%): rash (3.5%), depigmentation of skin (3.1%), itchy skin (2.0%).

• Immune-related pancreatitis (3.1%): persistent upper abdominal pain (sometimes worsened by diet), nausea, vomiting, and fatigue. You may have increases in laboratory tests for lipase and amylase. If you experience any of the above symptoms, you should notify your study doctor immediately.

• Immune-related hyperglycemia and diabetes (0.3%): increased blood glucose with weight loss, increased urination, increased thirst, and increased hunger. Immune-related diabetes requires insulin injections. If you experience any of the above symptoms, please inform your study doctor immediately.

• Immune-related hypophysitis (0.2%): hypophysitis is a decrease in the amount of hormones secreted by the pituitary gland in the brain. Symptoms include headache, thirst, visual impairment or double vision, breast milk leakage or irregular menstruation in women.

• Immune-related adrenocortical dysfunction (0.5%): may cause abdominal pain, vomiting, muscle weakness, fatigue, depression, hypotension, weight loss, kidney problems, and the changes in mood and personality.

• Immune-related myocarditis (0.4%): symptoms may include chest pain, tachycardia or arrhythmia, shortness of breath, and swelling of the legs. If you develop these symptoms, please inform your study doctor immediately.

• Immune-related myositis (0.1%): symptoms may include muscle weakness, pain, and swelling. If you develop these symptoms, please inform your study doctor immediately.

Other Potential Immune-Related Adverse Reactions

Some immune-related side effects have not been identified in JS001 clinical trials but were observed in other similar marketed medicines. If you develop below symptoms, inform your study doctor immediately.

• Immune-related neurological side effects: Inflammation of the brain which may include headache, confusion, fever, memory problems or seizures. Rare symptoms of nervous system inflammation may include weakness in the legs, arms or face, numbness or tingling in the hands and feet. In very rare cases, inflammation of the nervous system can be severe, which may manifest as dysphagia, weakness and dyspnea in a short period of time.

• Immune-related nephritis: Inflammation of the kidneys which may include abnormal kidney function tests, changes in the amount or color of your urine.

• Immune-related eye toxicity: Inflammation of the eyes which may include changes in eyesight, eye pain or redness.

• Immune-related osteoarthritis: Symptoms which may include joint pain, joint swelling, joint effusion, and limited joint motion.

If there are suspected immune-related adverse reactions, the investigators may order diagnostic tests to understand the immune response and confirm the diagnosis. If your symptoms are found to be due to immune related adverse reactions, the investigators will give you treatment, which may include oral or intravenous dose of corticosteroids or immunosuppressants according to the specific situation and severity. Even though thesymptoms have resolved, the dose of corticosteroids needs to be reduced slowly to maintain its therapeutic effect and avoid recurrence or worsening of the symptoms.

Side Effects for Gemcitabine

- Pulmonary toxicity (to be poisonous to the lung),
- Myelosuppression including neutropenia, thrombocytopenia (low level of blood platelet), and anemia,
- Haemolytic-uremic syndrome (an acute illness related to the renal function) and/or renal failure,
- Serious hepatotoxicity (to be poisonous to the liver), including liver failure and death.

For more details regarding the safety information of gemcitabine, see the appropriated Package Insert.

Side Effects for Cisplatin

- Myelosuppression,
- Ototoxicity (to be poisonous to the ear),
- Nephrotoxicity (to be poisonous to the kidney).

For more details regarding the safety information of cisplatin, see the appropriated Package Insert.

Other Risks and Possible Discomfort

- Blood samples will be taken from a vein in your arm during the study. The taking of a blood sample may cause some discomfort and bruising, and there is a potential for infection. Other risks, although rare, include nerve damage, dizziness and fainting.
- You will have ECG during the study. Small sticky pads will be stuck to your chest, arms, and legs, and a machine will measure the electrical activity of your heart.

We may need to clip small patches of your hair in these areas. These sticky pads may cause some local irritation and may be uncomfortable to remove.

- Blood pressure and heart rate will be measured during the study. An inflatable cuff will be placed on your arm and a machine will measure your blood pressure and heart rate, after you have been sitting down for 10 minutes. You may experience mild discomfort in your arm while the cuff is inflated.
- A MRI scan is painless and will not expose you to X-ray radiation. A CT scan is a type of X-ray. Before these scans, a contrast medium may be injected into one of your veins. A contrast medium is like a dye that will spread through your body and will help give clearer images. The injection of contrast medium may cause some discomfort and bruising. There is a risk of potentially serious allergic reactions in some people who receive contrast medium. Some people may feel frightened by the cramped space inside the machine or by the loud, repeated sounds the machine makes. The greatest risk of having an MRI is the chance of metal objects flying through the air toward the magnet and hitting you. To reduce this risk, all people getting the MRI scan will be asked to remove all metal from their clothing and all metal objects from their pockets. Please inform the study doctor if you have metal in your body from an operation, since you may not be able to have a MRI scan. Also, if you have a pacemaker you should not have a MRI scan.
- You may have tumor sampling during the study in order to collect more information about your disease. During the sampling, you may experience minor local bleeding, pain at the needle site, redness at the needle site, swelling under the skin that contains blood (hematoma), and sleepiness if you choose to receive a "pain killer" and/or medicine to help you relax. Rare but serious reactions include infection; shortness of breath, slow heart rate, and low blood pressure if you choose to receive a "pain killer" and/or medicine to help you relax.
- A heparin/saline lock may be placed in a vein for Study Drug administration during the site visits. The risks of a heparin/saline lock include pain, bruising, clotting, bleeding and possible infection at the site of the heparin/saline lock placement. Saline (salt water solution) or heparin may be used to flush the heparin/saline lock to prevent clots from forming in the catheter.

Pregnancy and Breast-feeding

If you are or become pregnant, or if your partner becomes pregnant, there may be unknown risks to the baby. If you are a woman who may be able to have children, you will be given a pregnancy test at screening, and if the result is positive, you will not be able to be in the study. If you are a sexually-active man or woman, you must use an accepted form of birth control throughout the study and for at least 60 days after the last dose of the Study Drug. Acceptable birth control methods include double barrier method

and total abstinence. The study doctor will discuss methods of effective birth control with you if needed. If you become pregnant or think you may be pregnant during the study or within 60 days after the last dose of the Study Drug, stop using the Study Drug and contact the study doctor's office **immediately**. You may be asked to withdraw from the study. You must not be breast-feeding an infant during the study. If your partner becomes pregnant or thinks she may be pregnant during the study or within 60 days after the last dose of the Study Drug, contact the study doctor's office **immediately.**

The study doctor must follow up and keep a record of the course and the outcome of all pregnancies, even if you withdraw from the study or if the study has finished. If you or your partner becomes pregnant during the study, the study doctor or his/her staff will contact you/your partner and your/your partner's doctor for information about the pregnancy until clear pregnancy outcome.

9 WHAT ARE THE POSSIBLE BENEFITS?

We hope that the Study Drug will help your condition. Also, you might benefit from the chemotherapy (gemcitabine and cisplatin) for your disease. However, you may not get any direct benefit from taking part in this study. You will be given close attention from the study staff during the time you are involved in the study. You may get information about your health from physical examinations and medical tests done in this study.

This study will provide information about the safety and efficacy of the Study Drug, as well as the medical knowledge of your disease.

If the results of this study are positive and, along with extra studies, lead to approval by the regulatory authorities of China for use in humans, there may be benefits for patients in the future. These benefits may include improvement for the future treatment of people with recurrent or metastatic nasopharyngeal cancer, and profound understanding of the disease.

10 ARE THERE ALTERNATIVE TREATMENTS?

You do not have to be in this study to get treatment for your nasopharyngeal cancer. Other treatments include chemotherapy, targeted therapy, or radiation therapy. Other experimental treatments may also be available. You can discuss your treatment options with your doctor.

11 WILL I INCUR ANY EXPENSES OR RECEIVE ANY PAYMENTS?

There will be no cost to you or your insurance company for the study medication or the study-related procedures and examinations.

You will not be paid for your participation in this study. You may have some expenses from being in the study, such as bus fare or parking fees when you visit the study center. You will be paid 100 CNY per visit for these expenses.

The Sponsor is paying the study doctor and/or ***(name of Institution or site)*** for their work in this study.

12 WHAT IF I AM INJURED DURING THE STUDY?

If you experience any unexpected symptoms or injury, and if emergency medical treatment is required, please report it immediately to:

_____ (Site to insert contact name and number).

If you have a physical injury or illness directly related to the study medication or study procedure which was properly performed in accordance with the protocol (referred to as a study-related injury), medical treatment will be provided to you. You will not be charged for this treatment. The Sponsor will cover the cost of reasonable and necessary medical treatment for a study-related injury and has insurance to cover the study-related injury Study-related injuries do not include injuries that result from your own fault or intention. Additionally, payment for such things as lost wages, expenses other than medical care, or pain and suffering is not available.

13 WHAT WILL HAPPEN IF THERE IS ANY NEW INFORMATION?

If any new information becomes available which may influence your decision to stay in the study, you will be told in a timely manner.

14 WILL INFORMATION ABOUT ME BE KEPT CONFIDENTIAL?

By signing this form you consent to the study doctor and his or her staff collecting and using your personal data for the study. This includes: your age, sex, your ethnic origin, and information on your physical or mental health or condition.

The information shared with the Sponsor is protected by the use of a code, which is a number specifically assigned to you. The study doctor is in charge of the code needed to connect your data to you.

All medical records and research materials that identify you by name will be held confidential (confidential data) as permitted by law. However the study doctor, the

Sponsor and its representatives, the study monitor (who checks how the study is going and makes sure that the information is being collected properly) and, under certain circumstances, the regulatory authorities and ethics committees will be able to inspect confidential data that identify you by name.

All personal data from this study will be treated in accordance with national and local data protection laws.

By signing this consent form, you grant permission for medical information about you obtained during this study (your study data) to be made available to authorized representatives of the regulatory authorities and other government agencies. You also grant permission for your study data to be made available to the Sponsor, the study monitor, other study personnel, and ethics committees. The Sponsor may transfer your study data to countries outside of <<country, and if applicable the European Union (EU)>> for the purposes described in this document. Please be aware that the laws in such countries may not provide the same level of data protection as in <<country>> and may not stop your study data from being shared with others. The study doctor, the regulatory authorities, and the Sponsor may keep the study data indefinitely.

You have the right to request information about your study data held by the study doctor and the Sponsor. You also have the right to request that any inaccuracies in such data be corrected. If you wish to make a request, then please contact the study doctor, who can help you contact the Sponsor .

Your consent for the use of your study data as described above does not have an expiration date. If you withdraw your consent for participating in this study, your study data that were collected before you withdrew your consent may still be used as described above. Once you have withdrawn your consent for participating in the study, no further data will be collected about you for the purposes of this study unless you agree otherwise, for example, you agree to have further tests and examinations. If you do agree to have further data collected after you have withdrawn your consent, these study data may also be used as described above.

The results of this study may be published in a medical journal and shown at medical meetings. You will not be identified (by name or any other means, e.g., photo) in any of these publications.

(For trials in China, include: A description of this clinical trial will be available on www.chinadrugtrials.org.cn. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

For applicable clinical trials under a US Investigational New Drug (IND) application [or other FDA regulations] which are initiated on or after 07 March 2012, the following text is mandatory according to US CFR 50.25(c): “A description of this clinical trial will be

available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. (delete as applicable for countries not under US IND or other FDA regulations)."

For applicable clinical trials that are conducted in the EU and the European Economic Area (EEA) or Clinical trials conducted outside the EU / EEA that are part of an EU Paediatric Investigation Plan (PIP), include: "A description of this clinical trial will be available through the public website https://www.clinicaltrialsregister.eu. This website will include information on the trial and summary of the results, but will not include any information that can identify you. You can search this web site at any time.")

15 WHAT IF I HAVE QUESTIONS?

If you have questions about the study, or have a problem related to the study, you may contact the study doctor or his/her staff at the telephone number below.

Name:_____Telephone: (_____) _____

If you are calling after hours or on a weekend, you may contact the individual below.

Name:_____Telephone: (_____) _____

If you have questions about your rights as a research participant, you should contact the individual below.

(Note: Insert name of IRB/IEC chairperson and/or name of IRB/IEC, address, and telephone number.)

Name:_____Telephone: (_____) _____

Address: _____

16 CONSENT STATEMENT OF PATIENT

I have received verbal information on the above study and have read the attached written information. I have been given the chance to discuss the study and ask questions.

I voluntarily consent to participate in this study, including all assessments, lifestyle restrictions, birth control requirements, and taking of blood samples.

I consent to the remaining blood samples from the main study, which I will donate, being used as indicated in the text, and according to the options I have initialed/signed below:

If my blood sample remains after mandatory analysis, I agree to donate the remaining blood samples from the main study to be used for exploratory biomarker assay related to my nasopharyngeal cancer and/or its treatment	☐ *Yes*	☐ *No*	_____ *Initials of Patient*

I understand that I am free to withdraw at any time. I understand that if I choose to not participate or choose to withdraw, my current medical care will not be affected by this decision.

I agree that my primary doctor may be told of my participation in this study.

I agree that my primary doctor may be asked to give information about my medical history.

I agree that my personal data, including data relating to my physical or mental health or condition, and ethnic origin, may be used as described in this consent form.

I understand that I will get and may keep a copy of this signed and dated consent form.

By signing and dating this consent form, I have not given up any of the legal rights that I would have if I were not a participant in a medical research study.

_____	_____	_____	AM/PM	_____
Signature of Patient	Date (mm/dd/yyyy)	Time		Printed Name of Patient
_____	_____	_____	AM/PM	_____
Signature of Witness	Date (mm/dd/yyyy)	Time		Printed Name of Witness
_____	_____	_____	AM/PM	_____
Signature of Legally Acceptable Representative	Date (mm/dd/yyyy)	Time		Printed Name of Legally Acceptable Representative

The relationship between the Patient and the Legally Acceptable Representative: _____

17 STATEMENT OF PERSON CONDUCTING INFORMED CONSENT DISCUSSION

I, the undersigned, certify that to the best of my knowledge, the patient signing this consent form had the study fully and carefully explained and clearly understands the nature, risks, and benefits of participation in this research study.

			AM/PM	
Signature of Investigator (or other Person Obtaining Consent)	Date (mm/dd/yyyy)	Time		Printed Name of Person Obtaining Consent

Only needs when treatment is continued after disease progress

Treatment Through Progression Consent Form

- I have read the information regarding “Initial Radiographic Disease Progression” of this Informed Consent Form. I have received answers to all of my questions about this study.
- I agree to receive continued study treatment and follow-up on time in the study and to receive the appropriate examinations. I will comply with the requirements of the study, and fully cooperate with the study doctor, truthfully and objectively provide information about my health and related conditions before participating in the study, during the study, and in the follow-up period to study personnel.
- I also understand that I can withdraw from the study at any time, which will not have any negative effects on my subsequent treatment. I understand that the Sponsor and my study doctor have the right to terminate the study at any time in my circumstances.
- I freely agree to participate in this research study as described and understand that I am free to withdraw at any time during the research study without affecting my future health care.
- I agree to inform my primary doctor that I have participated in the study.
- I understand that I will receive a signed copy of this consent form.
- I agree that my medical health data collected as part of this medical research study can be used and published.
- After full consideration, I volunteer to participate in the clinical study and to maintain full cooperation with study doctor.

CONSENT STATEMENT OF PATIENT

			AM/PM	
Signature of Patient	Date (mm/dd/yyyy)	Time		Printed Name of Patient
			AM/PM	
Signature of Witness	Date (mm/dd/yyyy)	Time		Printed Name of Witness
			AM/PM	
Signature of Legally Acceptable Representative	Date (mm/dd/yyyy)	Time		Printed Name of Legally Acceptable Representative

The relationship between the Patient and the Legally Acceptable Representative: _____

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I, the undersigned, certify that to the best of my knowledge, the patient signing this consent form had the study fully and carefully explained and clearly understands the nature, risks, and benefits of participation in this research study.

			AM/PM	
Signature of Investigator (or other Person Obtaining Consent)	Date (mm/dd/yyyy)	Time		Printed Name of Person Obtaining Consent

PAREXEL International

Shanghai Junshi Biosciences Co., Ltd.

JS001-015-III-NPC

A Phase III, Randomized, Placebo-Controlled, Multicenter, Double-Blind Study Comparing Toripalimab Injection (JS001) Combined with Chemotherapy versus Placebo Combined with Chemotherapy for Recurrent or Metastatic Nasopharyngeal Cancer

Statistical Analysis Plan

PAREXEL Project Number: 237456

SPONSOR SIGNATURE PAGE

Approved by:

Xiongwen Tang Director, Biostatistics Shanghai Junshi Biosciences Co., Ltd.	Date

PAREXEL SIGNATURE PAGE

Signatures below confirm that the review process has been completed in accordance with SOP-GDO-WW-019.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	Sean Chang Project Role: Biostatistics Lead

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CBC	Complete blood cell
CI	Confidence interval
CR	Complete response
CT	Computed tomography
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DoR	Duration of response
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ENR	Enrolled Set
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed consent form
iDMC	Independent Date Monitoring Committee
INR	International normalized ratio
IRC	Independent Review Committee
irRECIST	Immune-related Response Evaluation Criteria In Solid Tumors
ITT	Intent-to-treat
IWRS	Interactive Web response system
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NPC	Nasopharyngeal carcinoma
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic(s)
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-ligand 1
PFS	Progression-free survival
PK	pharmacokinetics
PPS	Per-protocol analysis set
PR	Partial response
PRO	Patient-reported outcomes
PT	Prothrombin time
Q3W	Every 3 weeks
QoL	Quality of life
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
Sd	Standard deviation
SD	Stable disease
ULN	Upper limit of normal

1 INTRODUCTION

This document presents the statistical analysis plan (SAP) for Junshi Protocol: A Phase III, Randomized, Placebo Controlled, Multicenter, Double-Blind Study Comparing Toripalimab Injection (JS001 or TAB001) Combined with Chemotherapy versus Placebo Combined with Chemotherapy for Recurrent or Metastatic Nasopharyngeal Cancer. This SAP contains definitions of analysis populations, derived variables, and statistical methods for the analysis of efficacy and safety parameters.

This SAP is based upon the following study documents:

- Study Protocol, Version 6.0 (Oct 14, 2020)
- Electronic Case Report Form (eCRF), Version 9.0 (Sep 11, 2020)

2 STUDY OBJECTIVES

Primary:

- To evaluate the efficacy of Toripalimab Injection (JS001) plus chemotherapy compared with placebo plus chemotherapy, as measured by independent review committee (IRC) – assessed progression-free survival (PFS) according to RECIST v1.1 in patients with histological/cytological confirmation of recurrent or metastatic nasopharyngeal carcinoma (NPC).

Secondary:

- To evaluate the efficacy of Toripalimab Injection (JS001) plus chemotherapy compared with placebo plus chemotherapy, as measured by overall survival (OS).
- To evaluate the efficacy of JS001 plus chemotherapy compared with placebo plus chemotherapy, as measured by investigator-assessed objective response rate (ORR), duration of response (DoR), disease control rate (DCR) according to RECIST v1.1.
- To evaluate the efficacy of JS001 plus chemotherapy compared with placebo plus chemotherapy, as measured by investigator-assessed PFS according to RECIST v1.1.
- To evaluate the IRC and investigator-assessed PFS rate at 1 and 2 years in each treatment arm.
- To evaluate the OS rate at 1 and 2 years in each treatment arm.
- To assess disease-related symptoms and HRQoL in patients treated with JS001 plus chemotherapy compared with placebo plus chemotherapy using the EORTC QLQ-C30, EORTC QLQ-H&N35 and ECOG performance status assessments.
- To evaluate the safety and tolerability of JS001 plus chemotherapy compared with placebo plus chemotherapy.
- To evaluate the incidence and titers of anti-drug antibodies (ADA) against JS001 and to explore the potential relationship of the immunogenicity response with pharmacodynamics, safety, and efficacy.

- To evaluate the efficacy of JS001 plus chemotherapy compared with placebo plus chemotherapy as measured by investigator and IRC-assessed PFS, ORR, DoR, and DCR according to irRECIST.

Exploratory:

- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers (including but not limited to PBMC, PD-L1, PD-1, tumor mutation burden and others) in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to Toripalimab Injection (JS001).
- To evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumor volume related to the immunomodulatory activity of JS001 (i.e., pseudoprogression and tumor immune infiltration) from true disease progression.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a randomized, placebo-controlled, multi-center, double blinded, Phase III study to determine the efficacy and safety of Toripalimab Injection (JS001) in combination with gemcitabine/cisplatin compared with placebo in combination with gemcitabine/cisplatin as first-line treatment in patients with histological/cytological confirmation of recurrent or metastatic NPC.

Approximately 280 patients who fulfill all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to one of the two treatment arms according to the following stratification factors:

- ECOG performance status (0 versus 1)
- Disease stage (recurrent versus metastatic)

After stratification, patients will be randomly assigned by Interactive Web Response System (IWRS) to the combination of JS001 (Arm A) or placebo (Arm B) with gemcitabine and cisplatin given every 3 weeks (Q3W) in 3-week cycles. Day 1 (baseline) will be defined as the first day a patient receives study medication. Patients will receive JS001 (Arm A) or placebo (Arm B) on Day 1 of each 3-week cycle. In Arms A & B, patients will receive gemcitabine on Days 1 & 8 and cisplatin on Day 1 of each cycle. The chemotherapy will continue until progressive disease, excessive toxicity, noncompliance, withdrawal of consent, or a maximum of 6 cycles, whichever occurs first in the 'during chemotherapy' phase. During the 'post-chemotherapy' phase, patients randomized to Arm A or Arm B will continue treatment with JS001 or placebo as maintenance therapy Q3W until excessive toxicity or progressive disease, withdrawal of consent or Investigator's judgement or a maximum of 2 years. Patients may continue treatment with JS001 (Arm A) or placebo (Arm B) beyond radiographic progression by the Response Evaluation Criteria In Solid

Tumors (RECIST) version 1.1, provided they are experiencing clinical benefit, as assessed by the Investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression, as determined by the Investigator after an integrated assessment of radiographic data and clinical status. Patients will be permitted by sponsor medical monitor or designee and treating physician to continue JS001/placebo after RECIST v1.1 criteria for progressive disease are met if they meet all of the criteria according to the protocol.

Tumor evaluation scans will be performed at screening (as baseline) then every 6 weeks in the first 12 months then every 9 weeks thereafter until objective disease progression. The management of patients will be based solely upon the results of the tumor evaluation scans conducted by the Investigator.

The IRC, consisting of independent experts, will review all radiologic scans according to RECIST 1.1 and irRECIST.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 32 months.

At the time of end of study, sponsor will continuously provide investigational product to patients who still are under treatment in accordance with local regulations.

This is a double blinded and one interim efficacy analysis of PFS is planned and pre-defined stopping boundary is set for two-sided p-value. The iDMC will provide the recommendation as to whether to unblind the study or not according to the data of interim analysis and the iDMC charter if the stopping boundary were met. If the Sponsor accepted the recommendation and unblind the study, JS001 will be provided to the patients who were randomized to arm A and still on JS001 treatment until the treatment discontinuation criteria are met according to protocol, the placebo treatment will be terminated for the patients who were randomized to arm B. After the study is unblinded, the tumor evaluation, survival follow-up, safety information, and so on information collection should be performed as required by the protocol.

Table 1. Schedule of Activities

	Screening [a]		All treatment cycles									Treatment Discontinuation [c]	Survival Follow-Up [d]
			During chemotherapy						Post chemotherapy		Unplanned Visit [b]		
Day (Window)	–28 to –1	–7 to –1	C1D1	C1D8	C2D1 (± 3)	C2D8	C3-C6D1 (± 3)	C3-C6D8	C7D1 (± 3)	C8D1 to PD or intolerable toxicity (± 3)	NA		
Informed consent	x[e]												
Demographic data	x												
Medical history and baseline conditions	x												
Patient-reported outcomes [f]			x		x		x		x	x			
Vital signs[g]		x	x	x	x	x	x	x	x	x	x	x	
Weight		x			x		x					x	
ECOG		x	x	x	x	x	x	x	x	x	x	x	
Height		x											
ECG[h]	x		As clinically indicated										
Echocardiogram[h]	x	As clinically indicated											
Complete physical examination [i]	x												
Limited physical examination [j]			x		x		x		x	x		x	
Hematology [k]		x		x	x	x	x	x	x	x		x	
Coagulation test (INR, PT, aPTT)		x	As clinically indicated										

	Screening [a]		All treatment cycles									Treatment Discontinuation [c]	Survival Follow-Up [d]
			During chemotherapy						Post chemotherapy		Unplanned Visit [b]		
Day (Window)	–28 to –1	–7 to –1	C1D1	C1D8	C2D1 (± 3)	C2D8	C3-C6D1 (± 3)	C3-C6D8	C7D1 (± 3)	C8D1 to PD or intolerable toxicity (± 3)	NA		
Chemistry [l]		x		x[m]	x	x[m]	x	x[m]	x	x		x	
Pregnancy test [n]		x			x		x		x	x		x	
TSH, free T3, free T4 [o]	x				x		x		x	x		x	
Urinalysis [p]		x			x		x		x	x		x	
HIV, HBV, HCV serology [q]	x												
EBV serology [r]			x [r]				x [r]		x [r]	x[r]			
Study drug administration			x	x	x	x	x	x	x	x			
Tumor response assessment	x[s]						x[t]		x[t]				
Serum sample for ADAs [u]			x				x		x			x	
Blood sample for biomarkers [v]			x				x		x				
Concomitant medications [w]		x	x	x	x	x	x	x	x	x	x	x	
Adverse events [x]	x		x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; eCRF = electronic Case Report Form; NA = not applicable.

Notes: All assessments should be performed within 28 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Visit not specified by the protocol. Assessments should be performed as clinically indicated.

[c] Patients who complete the treatment period will return to the clinic for a treatment completion visit within 30 days after the last dose of study drugs. Patients who discontinue study drug prematurely will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study drug; If the study drug infusion delayed and discontinued subsequently, and the interval between last dose of study treatment and decision of treatment discontinuation probably is near or longer than 30 days, the investigator should complete Treatment Discontinuation Visit as early as they can after patients formally withdrawal from study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[d] Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months (±7 days) after treatment discontinuation until death, loss to follow-up, withdrawal of consent or study termination by the Sponsor.

[e] Informed consent must be documented before any study-specific screening procedure is performed.

[f] Questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

[g] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] A twelve-lead ECG and Echocardiogram is required at screening and as clinically indicated thereafter.

[i] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells. Results for full blood count must be available before commencing an infusion (samples must have been obtained within 3 days prior to the infusion, except for C1D1).

[l] Chemistry panel (serum or plasma) includes glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. Results for chemistry tests must be available before commencing an infusion (samples must have been obtained within 3 days prior to the infusion, except for C1D1).

[m] Only BUN or urea, creatinine, ALT and AST are needed to be performed on day 8 of gemcitabine. Results must be available before commencing an infusion (samples must have been obtained within 3 days prior to the infusion, except for C1D1).

[n] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at each cycle during treatment (samples must have been obtained within 3 days prior to the infusion, except for C1D1). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[o] Thyroid function testing (TSH, free T3, free T4) collected at screening, and each cycle thereafter (samples must have been obtained within 3days prior to the infusion, except for C1D1).

[p] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs). Samples must have been obtained within 3 days prior to the infusion, except for C1D1.

[q] All patients will be tested for HCV and HIV prior to the inclusion into the study and HCV-positive and/or HIV-positive patients will be excluded from the clinical trial. HBV DNA must be collected before Cycle 1, Day 1 in patients who have positive serology for hepatitis B surface antigen or negative serology for hepatitis B surface antigen and positive serology for anti-HBc.

[r] EBV serology samples will be collected before infusion of C1D1 and every two cycles prior to the infusion for 12 months and then every 3 cycles prior to the infusion until disease progression, loss of clinical benefit, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. [s] Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRIs of the nasopharynx, neck, chest and abdomen. A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan.

[t] Tumor assessment should be done to evaluate the target, non-target, and new lesions, it will include all known sites of disease documented at screening, which include but not limit to CT scans (with oral/IV contrast unless contraindicated) or MRIs of the nasopharynx, neck, chest and abdomen, and the same radiographic procedure should be used throughout the study, bone scans should also be performed if clinically indicated. Perform every 6 weeks (± 7 days; approximately every two cycles) for 12 months following Cycle 1, Day 1 and then every 9 weeks (± 7 days) thereafter, regardless of treatment delays, until disease progression, loss of clinical benefit, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. CT scans may be repeated at any time if progressive disease is suspected.

[u] See Protocol Appendix 2 for detailed schedule.

[v] See Protocol Appendix 2 for detailed schedule.

[w] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug to the treatment discontinuation visit.

[x] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 60 days after the last dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

3.2 Efficacy and Safety Endpoints

3.2.1 Primary Efficacy Endpoint

- IRC-assessed Progression-Free Survival (PFS) according to RECIST v1.1

3.2.2 Secondary Efficacy Endpoints

- OS
- IRC-assessed ORR according to RECIST v1.1
- IRC-assessed DoR according to RECIST v1.1
- IRC-assessed DCR according to RECIST v1.1
- Investigator-assessed ORR according to RECIST v1.1
- Investigator-assessed DoR according to RECIST v1.1
- Investigator-assessed DCR according to RECIST v1.1
- Investigator-assessed PFS according to RECIST v1.1
- IRC-assessed PFS rate at 1 and 2 years
- Investigator-assessed PFS rate at 1 and 2 years
- OS rate at 1 and 2 years
- Patient-Reported Outcome (PRO) using EORTC QLQ-C30, EORTC QLQ-H&N35 and ECOG performance status assessments
- Anti-drug antibody
- PFS, ORR, DoR, and DCR according to irRECIST

3.2.3 Safety Endpoints

The following safety variables will be monitored and reported in the eCRF according to the study schedule (Table 1 in Section 3.1):

- The incidence of Adverse events (AEs)
- The incidence of serious adverse events (SAEs)
- Vital signs
- Physical examinations
- Laboratory variables
- 12-Lead Electrocardiogram (ECG) and Electrocardiogram

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2 General Presentation Considerations

'End of Study' is defined as the date of the last visit of the last patient, or the date of the last data point required for efficacy analyses or safety follow-up, whichever occurs later.

'Treatment Day' will be calculated relative to the first dose of study drug, i.e. Treatment Day = Assessment Date - The First Day a Patient Receives Study Medication + 1.

Continuous data will be summarized in terms of the mean, standard deviation (Sd), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The Sd will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.0001, in general, will be presented to four decimal places. P-values less than 0.0001 will be presented as "<0.0001".

Confidence interval (CI) will be presented to one more decimal place than the raw data.

All report outputs will be produced using SAS® version 9.3 or a later version in a secure and validated environment. All report outputs will be provided to the Sponsor in a single Microsoft Word document per each output.

Baseline for Efficacy and Safety

Baseline measurements are the last available data obtained prior to the first dose of study drug.

Scheduled and Unscheduled Assessments

Scheduled assessments taken outside of protocol allowable windows will be displayed according to the eCRF assessment recorded by the Investigator. The by-visit tables will only include the scheduled assessments, unless specifically stated otherwise. If more than one value is available for a given visit, the first valid observation will be used in summary tables, unless specifically stated otherwise, and all observations will be presented in listings.

Unscheduled assessments will be included in listings, but not in summary tables.

Missing Data Conventions

In general, missing data will not be imputed for both efficacy analysis and safety analysis, unless specifically stated otherwise.

Detection of Outliers

Any outliers that are detected during the review of the data before database lock will be investigated. If necessary, queries will be issued to the Investigator, to either correct or confirm the outlier.

4.3 Study Subjects

4.3.1 Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion.

The following summaries will be provided:

- A summary of the number and percentage of patients who were randomized, the number and percentage of patients who were excluded prior to randomization by major reason and overall, and the number of percentage of patients who were re-screened, using the Enrolled Population.
- A summary of the number and percentage of patients who were treated (with at least one dose of study drug) in each phase of the study (during-chemotherapy phase and post-chemotherapy phase) and the number and percentage of patients who were discontinued from treatment in each phase of the study (during-chemotherapy phase and post-chemotherapy phase), and the number and percentage of major reason of patient discontinuation from treatment in each phase of the study (during-chemotherapy phase and post-chemotherapy phase), by treatment arm and overall, using the ITT population .
- A summary of the number and percentage of patients completed the study and discontinued from the study, and the number and percentage of major reason of patient discontinuation from the study, by treatment arm and overall, using the ITT population.
- A summary of follow-up time (months), which is defined as the time from randomization to a specified event (death, end of the study or the data cut-off for the analysis, whichever occurs first), by treatment arm and overall, using the ITT population. The study follow-up time (months) is calculated as

(event date - randomization date + 1) / 30.4375

A by-patient listing of disposition data will be provided, using the Enrolled Population.

4.3.2 Protocol Deviations

Protocol Deviations will be classified as “major” or “minor”, and any action to be taken regarding the exclusion of patients or affected data from specific analyses will be defined in the project-specific Protocol Deviation Specification.

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the patient’s rights, safety, well-being, and/or on the validity of the data for analysis.

A summary of the number and percentage of patients with major protocol deviations by treatment arm and overall, and type of deviation will be provided, using the ITT population.

A by-patient listing of protocol deviations will be provided using the ITT population.

4.4 Analysis Populations

4.4.1 Enrolled Population

Enrolled population is defined as all patients who provided informed consent from (ICF) for this study.

4.4.2 Intent-to-Treat (ITT) Population

The intent-to-treat set (ITT) will include all patients randomized. Patients will be analyzed according to the study arm to which they are randomized.

4.4.3 Per-Protocol Analysis Set (PPS)

The Per-Protocol Analysis Set (PPS) will include all ITT patients who do not have any major protocol violations which may have potential impact on the key efficacy or safety endpoints. Major protocol violations will be defined and inclusion of subjects in the PPS population will be finalized prior to study unbinding. Patients will be analyzed according to the study arm to which they are randomized. The PPS population will be used for some secondary/exploratory analysis as well as sensitivity analysis of the primary efficacy endpoints.

4.4.4 Safety Population

The safety population will include all patients who receive any amount of JS001 or placebo. Patients who are randomized into the study but did not receive any amount of study drug will not be included in the safety population.

A summary of the analysis populations and the set will be provided.

4.5 Demographic and Other Baseline Characteristics

Patient demographic and baseline characteristics will be summarized by treatment arm using the ITT population.

Following summaries will be provided:

- A summary of demographic data and baseline characteristics by treatment arm, including age, sex, ethnicity, race, baseline height (cm), baseline weight (kg), baseline ECOG performance status, baseline disease stage, smoking history, and alcohol use.
- A summary of medical history by treatment arm, system organ class, and preferred term, coded by Medical Dictionary for Regulatory Activities (MedDRA) version 23.0
- A summary of nasopharyngeal carcinoma (NPC) diagnosis.

Age will be calculated as the number of complete years between a patient's date of birth and the date of informed consent. Age (in years) will be calculated as:

(Date of informed consent – date of birth + 1)/365.25

If date of birth is a partial date missing month only, month will be assumed to be June. If date of birth is a partial date missing day only, day will be assumed to be 15th of the month. If date of birth is a partial date missing both month and day, it will be assumed to be Jun 30 of the year.

Following listings will be provided:

- A by-patient listing of demographic and baseline characteristics
- A by-patient listing of medical history will include reported term, coded term, onset date, ongoing (yes, no), and date of resolution
- A by-patient listing of NPC diagnosis
- A by-patient of tumor tissue

4.5.1 Nasopharyngeal Carcinoma Diagnosis

A summary of nasopharyngeal carcinoma (NPC) diagnosis will be provided using the ITT population, and a by-patient listing of NPC diagnosis will be provided as well.

For the nasopharyngeal carcinoma diagnosis, the histology information recorded in the CRF of "Other" and "Unknown" is diverse therefore the data are manually reviewed and further categorized into "Nasopharyngeal carcinoma, unclassified", "Non-keratinizing squamous cell carcinoma, undifferentiated", "Non-keratinizing carcinoma, unclassified", or "Other (please see Section 6.2 Appendix C).

4.5.2 Previous Systemic Therapy

A summary of previous systemic therapy categorized by anatomical therapeutic chemical (ATC) and preferred name using the ITT population will be provided.

The systemic therapies will be coded using the WHODrug Dictionary.

A by-patient listing of previous systemic therapy will be provided.

4.5.3 Previous Radiation Therapy

A summary of number and percentage of patients received previous radiation therapy, location, total dose (in centigrays), therapy category, mode of radiation therapy, and best response using the ITT population will be provided.

A by-patient listing of previous radiation therapy will be provided.

4.5.4 Concomitant Radiotherapy

A summary of number and percentage of patients with concomitant radiotherapy during the study, location, total dose (in centigrays), therapy category, and intent of therapy, using the ITT population will be provided.

A by-patient listing of concomitant therapy will be provided.

4.5.5 Previous and Concomitant Medication

Previous and concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) are those used by a patient from 7 days prior to initiation of study drug to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Previous and Concomitant Medications eCRF.

The medications will be coded using the WHODrug Global Dictionary version Mar 2020 B3.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

Following summaries will be provided using the ITT population:

- A summary of concomitant medications categorized by anatomical therapeutic chemical (ATC) and preferred name
- A summary of previous medications categorized by ATC drug class and PT

A by-patient listing of previous and concomitant medications will be provided, including drug name, indication, dose, unit, frequency, route, start date, and stop date will be provided.

4.5.6 Previous and Concomitant Surgery

The surgeries will be coded using the MedDRA version 23.0. Whether the surgery is considered as previous or concomitant, including the handling of missing or partial start date and stop date, will follow the same rule to the medication (see section 4.5.5).

Following summaries will be provided using the ITT population:

- A summary of concomitant surgeries categorized by system organ class and preferred term
- A summary of previous surgeries categorized by system organ and preferred term

A by-patient listing of previous and concomitant surgery, including surgery description, surgery date, indication, and cancer related flag (yes, no) will be provided.

4.5.7 Concomitant Procedure

The concomitant procedure will be coded using the MedDRA version 23.0.

- A summary of concomitant procedure categorized by system organ class and preferred term will be provided

A by-patient listing of concomitant procedure, including procedure description, start/end date, and indication will be provided.

4.5.8 Post Anti-Cancer Therapy

Post anti-cancer therapy will be coded using the WHODrug Global Dictionary version Mar 2020 B3.

- A summary of post anti-cancer therapy categorized by system organ class and preferred name will be provided using the ITT population .

A by-patient listing of post anti-cancer therapy will be provided.

4.6 Extent of Exposure

The duration of exposure is defined as the duration from the first dosing date to the last dosing date of JS001/placebo and chemotherapy (gemcitabine or cisplatin) at the end of treatment. Duration of exposure (in weeks) will be calculated as:

(the last dosing date at the end of treatment – the first dosing date + 21) / 7

The actual cumulative total dose of JS001 received (mg) is defined as the summation of all actual total dose administrated from the first dosing date to the last dosing date at the end of treatment. For cisplatin and gemcitabine, the actual cumulative total dose received will be calculated cumulatively based on the data from CRF Drug Administration (Cisplatin/Gemcitabine): "Actual total dose administered".

Dose intensity will be calculated as:

actual cumulative total dose received/ duration of exposure

and relative dose intensity will be calculated as:

(actual cumulative total dose received / planned cumulative total dose received)×100%

where the planned cumulative total dose of JS001 received will be calculated according to the Q3W schedule (i.e. every 3 weeks) using the duration of exposure:

Round down of [duration of exposure (in weeks) / 3] to integer * 240 mg

For cisplatin and gemcitabine, the planned cumulative total dose received will be calculated cumulatively based on the data from CRF Drug Administration(Cisplatin/Gemcitabine): "Planned total dose administered".

A summary of the number of cycles received (number and proportion of patients), actual duration of treatment, actual cumulative total dose received per patient (mg), dose intensity, and relative dose intensity, weeks and number of cycles for chemotherapy will be provided by treatment arm, using the Safety Population.

Following listings will be provided using the Safety Population:

- A by-patient listing of administrations of study drug, including study drug administration (yes, no), reason for no administration, delayed administration (yes, no), reason for delay, start date and start time of administration, end date and end time of administration, actual total dose administrated, infusion temporarily interrupted/discontinued (interrupted, discontinued, no), reason for interrupted/discontinued.
- A by-patient listing of administrations of chemotherapy (gemcitabine/cisplatin), including drug administration (yes, no), reason for no administration, delayed

administration (yes, no), reason for delay, start date and start time of administration, end date and end time of administration, dose level, planned and actual total dose administrated, dose change (no change, dose decreased), reason for dose change, infusion temporarily interrupted/discontinued (interrupted, discontinued, no), reason for interrupted/discontinued.

4.7 Efficacy Evaluation

All efficacy summaries and analyses will be based upon the ITT population unless otherwise indicated. A by-patient listing for survival outcomes, a by-patient for tumor response assessment, and a by-patient listing for tumor assessment results by visit will be provided.

4.7.1 Analysis and Data Handling

This study is designed to test for superiority. The null hypothesis for the treatment comparison will be that there is no difference between JS001 in combination with chemotherapy (Arm A) and placebo in combination with chemotherapy (Arm B) for the primary endpoint PFS. The alternative hypothesis will be that there is a difference. Symbolically, this is expressed as follows:

$$H_0: S_A(t) = S_B(t) \text{ versus } H_1: S_A(t) \neq S_B(t)$$

where $S_A(t)$ and $S_B(t)$ are the survival distribution function of PFS for Arm A and Arm B, respectively.

The study has crossed the O'Brien-Fleming boundary for the planned interim analysis of IRC-assessed PFS, with a data cutoff date of 30 May 2020, when 128 IRC-assessed PFS events had been observed in the ITT population. The key secondary efficacy endpoints, including IRC-assessed objective response rate (ORR) and overall survival (OS), were to be tested hierarchically under a two-sided alpha level of 0.05. ORR was formally tested and reached its statistical significance at the interim analysis of PFS. OS will then be formally tested when 130 deaths are observed in the ITT population.

4.7.1.1 Adjustments for Covariates

The primary and secondary efficacy analyses of PFS and OS will be stratified by ECOG performance status (0 vs. 1), and disease stage (recurrent vs. metastatic).

4.7.1.2 Handling of Dropouts or Missing Data

In general, no imputation will be performed for missing data, unless specifically stated otherwise.

4.7.1.3 Multiple Comparisons/Multiplicity

No multiple comparisons will be performed in the study.

4.7.1.4 Examination of Subgroups

The primary efficacy endpoint of investigator-assessed PFS according to RECIST v1.1 will be analyzed including but not limited to following subgroups:

- Age: <=50 versus >50
- Sex: Male versus Female
- Baseline ECOG status per CRF: 0 versus 1
- Baseline ECOG status per IWRS: 0 versus 1
- Disease stage per CRF (recurrent versus metastatic)
- Disease stage per IWRS (recurrent versus metastatic)
- EBV copy number: <=500 versus >500; <=2000 versus >2000
- Baseline PD-1 expression status: PD-1 will be categorized to <=1% vs. > 1%, <=5% vs. > 5%, and <=10% vs. > 10%.

4.7.2 Primary Efficacy Endpoint – IRC-Assessed PFS

PFS is defined as the time from randomization to the time of first documented disease progression, as determined by IRC assessments per RECIST v1.1, or death from any cause, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment and no death will be censored on the date of randomization. For patients who do not experience disease progression but have started any new anti-tumor therapy, PFS will be censored at the time of the last tumor assessment before the new therapy. For patients who have two or more consecutive missing tumor assessments, PFS will be censored at the time of the last available tumor assessment before the missing, or at the date of randomization if there was no post-baseline tumor assessment before the missing. In the COVID-19 pandemic period, for patients who have two or more consecutive missing tumor assessments due to COVID-19, in the circumstance if subsequent tumor assessments become available and there is no immediate disease progression, the subsequent tumor assessments will be used in the PFS analysis; if the subsequent immediate tumor assessment is disease progression, PFS will still be censored at the last tumor assessment before the missing, or at the date of randomization if there is no post-baseline tumor assessment before the missing.

PFS (month) will be calculated as:

(event date or censoring date – randomization date + 1) / 30.4375.

If the day of death is missing, it would be imputed with day 15.

The two-sided log-rank test, stratified by ECOG performance status (0 vs. 1), and disease stage (recurrent vs. metastatic), as recorded in the IWRS, will be used as the primary analysis to compare PFS between the two treatment arms.

The hazard ratio (HR) for disease progression or death will be estimated with the use of the stratified Cox proportional hazards model by including strata of ECOG performance status (0 vs. 1), and disease stage (recurrent vs. metastatic). Efron's method will be used

to handle ties. The 95% CI for the HR will be constructed. Results from an unstratified analysis will also be provided.

The Kaplan-Meier methodology will be applied to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be developed. The Brookmeyer Crowley methodology[4] by using log-log transformation to survival function, will be used to construct the 95% CI for the median PFS for each treatment arm.

Primary analysis will be performed using ITT population. Sensitivity analysis will be performed using PPS as well.

4.7.3 Secondary Efficacy Variables

4.7.3.1 Investigator-Assessed PFS

IRC-assessed PFS is defined as the time from randomization until the earliest occurrence of disease progression, as determined by the independent review committee, per RECIST v1.1, or death from any cause, whichever occurs first.

The methods outlined for the investigator-assessed PFS will be used for the IRC-assessed PFS analysis.

4.7.3.2 Overall Survival (OS)

OS is defined as the time from randomization to death from any cause. Data from patients who are alive at the time of the analysis will be censored as of the last date they are known to be alive. OS (month) is calculated as:

(death date or censoring date – date of randomization + 1) / 30.4375

If the day of death is missing, it would be imputed with day 15.

The methods outlined for PFS will be used for the OS analysis.

A by-patient listing of survival follow-up status will be provided.

4.7.3.3 Objective Response Rate (ORR)

An objective response is defined as either a confirmed complete response (CR) or a partial response (PR), as determined by IRC and the investigator using RECIST v1.1. Patients not meeting these criteria, including patients without any post baseline tumor assessment, will be considered non-responders.

Any tumor assessment, either by the IRC or the investigator, after the first PD or the new anti-cancer therapy will not be used to determine the best overall response evaluation.

ORR is defined as the proportion of patients who had an objective response. ORR and its 95% CI will be calculated for each treatment arm, and its 95% CI will be constructed using the Clopper-Pearson method (Clopper and Pearson, 1934).

Treatment difference in ORR will be analyzed using the Cochran-Mantel-Heanszel test, stratified by ECOG performance status (0 vs. 1), and disease stage (recurrent vs. metastatic). The 95% CI for the difference in ORRs between the two treatment arms will be determined using the Mantel-Heanszel method.

4.7.3.4 Duration of Response (DoR)

DoR will be assessed in patients who have an objective response CR/PR as determined by IRC and the investigator using RECIST v1.1.

DoR is defined as the time interval from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease or death is documented, whichever occurs first.

Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments are performed after the date of the first occurrence of a CR or PR, duration of response will be censored at the date of the first occurrence of a CR or PR. The DoR (month) will be calculated as:

(progression date or censoring date – first date of CR or PR + 1) / 30.4375

The methods outlined for PFS will be used for the DoR analysis.

4.7.3.5 Disease Control Rate (DCR)

DCR is defined as the rate of patients with CR or PR as best response or stable disease (SD) maintained for 6 weeks (>= 6 weeks) as determined by IRC and the investigator according to RECIST v1.1.

The methods outlined for ORR will be used for the DCR analysis.

4.7.3.6 PFS rate at 1 and 2 years

The PFS rate at 1 and 2 years after randomization will be estimated with the use of the Kaplan-Meier methodology for each treatment arm, along with 95% CI that are calculated with use of the standard error derived from Greenwood's formula, where the PFS is the IRC and investigator-assessed PFS according to RECIST v1.1. The 95% CI for the difference in the PFS rate between the two treatment arms will be estimated with use of the normal approximation method.

4.7.3.7 OS rate at 1 and 2 years

The methods outlined for the PFS rate will be used for the OS rate analysis.

4.7.3.8 Patient-Reported Outcomes (PRO)

The EORTC QLQ-C30 and QLQ-H&N35 data will be scored according to the EORTC scoring manual, the scoring can be seen in Section 6.1 6.1Appendix A.

In the event of incomplete data, if the scale has more than 50% of the constituent items completed, a pro-rated score will be computed that is consistent with the scoring manual and the validation papers of the measure. For subscales with less than 50% of the items completed, the subscale will be considered missing.

Summary statistics (mean, Sd, median, and range) of absolute scores and mean changes from the baseline will be calculated for all disease and/or treatment related symptom items and subscales of the EORTC QLQ-C30 and QLQ-H&N35 at each assessment time point for each treatment arm during the administration of the treatment and the survival follow up period.

The mean (and 95% CI) and median of the absolute scores and the changes from the baseline will be reported for interval and continuous variables.

Previously-published minimally-important differences will be used to identify meaningful change from the baseline within each treatment arm on the disease and/or treatment related symptoms scales (Osoba et al., 1998).

Questionnaire completion rate for EORTC-QLQ-C30 and QLQ-H&N35 is defined as the proportion of questionnaires actually received out of the expected number (i.e., number of patients during the administration of the treatment), which will be calculated and summarized for each assessment time point by treatment arm.

Following listings will be provided:

- A by-patient listing of EORTC-QLQ-C30
- A by-patient listing of QLQ-H&N35

4.8 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Population unless otherwise indicated.

4.8.1 Adverse Events

AEs will be coded using the MedDRA version 23.0.

Treatment-emergent adverse events will be tabulated and are defined as those adverse events that either start or worsen in severity on or after the date/time of first dose of study treatment and on or before 60 days after the date/time of last dose of study treatment.

Where dates are missing or partially missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to

suggest that the adverse event started prior to the first dose of study treatment or more than 60 days after the last dose of study treatment.

The incidence of some AEs, which should have been summarized under the same preferred term, could be underestimated because they were coded to different preferred terms due to different reported terms. Aside from the MedDRA dictionary, additional aggregation rule are applied to the following AEs: Leukopenia, Neutropenia, Thrombocytopenia, Lymphopenia, Hypokalemia, Fatigue, Rash, Musculoskeletal pain, Cough, Diarrhea, Pneumonia, Neuropathy peripheral, Upper respiratory tract infection, Abdominal pain, Arrhythmia, Oedema, Proteinuria, Hypertension, Blood bilirubin increased, Insomnia (please see Section 6.4 Appendix D).

Following summaries will be provided:

- An overview of all TEAEs: the number and percentage of patients with any TEAEs, any >= grade 3 TEAE, any treatment-emergent immune-related adverse event (irAE), any treatment emergent adverse events of special interest (AESI), any >= grade 3 treatment-emergent AESI, any SAE, any TEAEs with relationship to study drug, any TEAEs with relationship to gemcitabine, any TEAEs with relationship to cisplatin, any TEAEs leading to drug withdrawn, any TEAEs leading to drug interruption, any TEAEs leading to dose reduced, and any TEAEs leading to death, by treatment arm
- A summary of the number and percentage of patients reporting a TEAE and the number of TEAEs, by treatment arm, system organ class, and preferred term
- A summary of the number and percentage of patients reporting a TEAE, by treatment arm, maximum severity (grade 1-2, grade 3, grade 4, grade 5, >= grade 3), system organ class, and preferred term
- A summary of the number and percentage of patients reporting a treatment-emergent irAE and the number of irAEs, by treatment arm, system organ class, and preferred term
- A summary of the number and percentage of patients reporting a treatment-emergent irAE, by treatment arm, maximum severity (grade 1-2, grade 3, grade 4, grade 5, >= grade 3), system organ class, and preferred term
- A summary of the number and percentage of patients reporting a study drug related TEAE and the number of study drug related TEAEs, by treatment arm, system organ class, and preferred term
- A summary of the number and percentage of patients reporting a study drug related TEAE, by treatment arm, maximum severity (grade 1-2, grade 3, grade 4, grade 5, >= grade 3), system organ class, and preferred term
- A summary of the number and percentage of patients reporting a gemcitabine related TEAE and the number of gemcitabine related TEAEs, by treatment arm, system organ class, and preferred term
- A summary of the number and percentage of patients reporting a cisplatin related TEAE and the number of cisplatin related TEAEs, by treatment arm, system organ class, and preferred term

- A summary of the commonly occurring TEAEs, i.e., reported in at least 5% of patients in any treatment arm, by treatment arm, system organ class, and preferred term
- A summary of the number and percentage of patients reporting a treatment emergent AESI and the number of AESI, by treatment arm, system organ class, and preferred term
- A summary of the number and percentage of patients reporting a severe TEAE (AE with grade equal to or greater than 3) and the number of severe AEs, by treatment arm, system organ class, and preferred term
- A summary of the number and percentage of patients reporting an TEAE leading to infusion reaction, by treatment arm, system organ class, and preferred term
- A summary of the number and percentage of patients reporting the TEAE leading to death, by treatment arm, system organ class, and preferred term

For the summarization of number of patients, a patient will be counted only once for each system organ class and each preferred term, even if the patient reported one or more event under each subcategory; for the summarization of number of events, the number of AEs will count all AEs of each patient under each system organ class and each preferred term.

Unless specified otherwise, the table of a summary will be ordered in terms of decreasing number of patients for MedDRA system organ class and then preferred term within system organ class in the overall group.

For each AE, severity will be graded based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, and the most extreme grade recorded in eCRF will be attributed and used in the by-severity summaries. If the severity is missing, it will not be imputed. Besides, if relationship to study drug or chemotherapy (gemcitabine, cisplatin) is missing, the relationship will be imputed as Yes.

Following listings will be provided:

- A by-patient listing of all AEs
- A by-patient listing of all immune-related AEs

By-patient listings will be presented by treatment arm and will include: center, patient identifier, age, sex, race, adverse event (system organ class, preferred term, and verbatim term), AE start date, AE stop date, severity, serious (yes, no), seriousness criteria, relationship (study drug, gemcitabine, cisplatin), causality, action taken, outcome, infusion reaction (yes, no) and timepoint of AE occurrence if yes (during infusion, with 24 hours after end of infusion).

4.8.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death).

- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death).
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11 of the protocol).
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

Other significant adverse events are those adverse events reported as leading to an intervention e.g. discontinuation of study treatment.

Following summaries will be provided:

- A summary of the number and percentage of deaths during the study treatment period, and the number and percentage of deaths during the follow-up period after treatment completion/discontinuation, by treatment arm
- A summary of the number and percentage of patients reporting a SAE and the number of SAEs, by treatment arm, system organ class and preferred term

4.8.3 Vital Signs and Weight

Vital signs will include pulse rate (beats/minute), respiration rate (breaths/min), systolic and diastolic blood pressure (mmHg) while the patient is in a seated position, and temperature (˚C). Vital sign will be measured and the relevant assessment will be performed at the period of pre-dose, JS001 infusion, and post-dose, respectively.

Both raw values and changes from baseline will be summarized using descriptive statistics at each scheduled visit by treatment arm. Baseline is defined as the last evaluation prior to the first dose of study drug.

Vital sign assessment will be summarized using frequencies and percentages.

Following summaries will be provided:

- A summary of the observed values and changes from baseline for each vital sign by each period (i.e. pre-dose, JS001 infusion, and post-dose) and by visit and treatment arm
- A summary of vital sign assessment by each period (i.e. pre-dose, JS001 infusion, and post-dose) and by visit and treatment arm.
- A summary of weight and change from baseline by visit and treatment arm.

If vital sign data is missing, no imputation will be made. During the study, the measurement of vital signs may be repeated at the discretion of the Investigator for safety reasons. If

repeat measurements are taken at a particular time point, the last valid measurement will be used in the summaries.

By-patient listings of vital signs and weight will be provided.

4.8.4 Physical Examinations

A complete physical examination, according to local practice, should be performed at the screening visit, which includes

- head, eyes, ears, nose, and throat
- cardiovascular
- dermatological
- musculoskeletal
- respiratory
- gastrointestinal
- genitourinary
- neurological systems
- cranial nerve
- Lymph node (head and neck)
- Lymph node (other than head and neck)

At subsequent visits, only limited, symptom-directed physical examinations will be performed.

Following summaries will be provided:

- A summary of the number and percentage of patients for the complete physical examination at the screening visit will be provided by category (normal, abnormal and clinically significant, abnormal but not clinically significant), body system, and treatment arm.
- A summary of the number and percentage of patients for any abnormal findings in the subsequent visits will be provided by category (abnormal and clinically significant, abnormal but not clinically significant), visit, and treatment arm.

By-patient listings of physical examination will be provided.

4.8.5 Laboratory Evaluation

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)

- Coagulation (INR, PT, aPTT)
- Serum pregnancy test should only be conducted at screening period for women of childbearing potential, including women who have had a tubal ligation; urine pregnancy tests will be performed at each cycle during treatment. A serum pregnancy test must be performed if the urine pregnancy test is positive.

  Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy or not being postmenopausal (≥12 months of amenorrhea).
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood), dipstick permitted, and microscopic examination (RBCs, WBCs).
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)
- HBV serology (HBsAg, HBsAb, HBcAb)
- HBV DNA should be obtained prior to randomization if patient has positive serology for HBcAb or HBsAg.
- HCV serology (HCV antibody)
- HCV RNA if HCV antibody is positive.
- HIV testing
  All patients will be tested for HIV prior to the inclusion into the study and HIV positive patients will be excluded from the clinical trial.

The continuous test results for each test parameter and change from baseline by visit will be summarized using the descriptive statistics. The categorical test results for each test parameter will be summarized using frequencies and percentages. A shift table of the categorical test results at each visit compared to the categorical test results at baseline will be provided.

The toxicity grade and abnormality worsened from the baseline will be summarized according to NCI-CTCAE version 5.0 (please see Section 6.2 Appendix B).

A by-patient listing of all laboratory data will be provided by treatment arm.

4.8.6 12-Lead Electrocardiogram (ECG) and Echocardiogram

Frequency and percentage of patients who had abnormal (clinically significant or not clinically significant) ECG and echocardiogram overall assessment will be summarized by treatment arm. When there are multiple ECGs taken at a visit, the worst ECG overall assessment will be used.

By-patient listings of 12 ECG and echocardiogram, including the LVEF result (%), will be provided.

4.8.7 ECOG Performance Status

Following summaries will be provided:

- A summary of the number and percentage of patients for each ECOG performance status score by visit, and treatment arm.
- A shift summary of baseline score by maximum post-baseline score by treatment arm

A by-patient listing of ECOG performance status at each visit will be provided.

4.8.8 Pregnancy Test

A by-patient list of pregnancy test results will be provided only for female patients.

4.9 Other Evaluation

4.9.1 Sensitivity Analyses for IRC-Assessed PFS

The following analyses will be performed as the sensitivity analyses for the primary analysis of investigator-assessed PFS:

- The unstratified analysis in which the log-rank test will be performed at two-sided alpha level of 0.05, the HR will be estimated using the proportional hazards model. Efron's method will be used to handle ties. The 95% CI for the HR will be constructed.
- The analysis using the methods outlined for the primary analysis in which the stratification factors are the actual variables recorded in CRF rather than the stratification factors recorded in the IWRS.
- The analysis using the methods outlined for the primary analysis in which patients did not experience disease progression or death but started new anti-tumor therapy whose event date is defined as the start date of new treatment.
- The analysis using the methods outlined for the primary analysis in which patients with disease progression or death being documented after missing two consecutive tumor assessments will be handled as event and will not be censored.
- The analysis using the methods outlined for the primary analysis. Regardless patients with disease progression or death being documented after missing two consecutive tumor assessments due to COVID-19, PFS will be censored at the last tumor assessment before the missing, or at the randomization date if there was no post-baseline tumor assessment before the missing.
- The analysis using the methods outlined for the primary analysis in which the analysis population is the PPS.

4.9.2 PFS, ORR, DoR, and DCR per Immune-Related RECIST

Analyses using irRECIST for PFS, ORR, DoR and DCR as determined by the IRC and investigator will be conducted. The applicable methods outlined for PFS and ORR will be used for these analyses.

The ORR and its 95% CI will be calculated, and its 95% CI will be constructed using the Clopper-Pearson method (Clopper and Pearson, 1934).

All results of analysis will be summarized using the ITT population .

4.9.3 Subgroup Analyses

To assess the consistency of the study results, the IRC and investigator-assessed PFS will be analyzed according to the subgroups defined in Section 4.7.1.4.

Summaries of PFS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median PFS, will be produced separately for each level of the categorical variables for the comparisons between treatment arms.

Subgroup analyses will be performed using ITT population.

4.9.4 Immunogenicity Analysis

Anti-JS001 antibodies, immunoglobulins, and JS001 plasma level will be summarized with descriptive statistics by treatment arm using the Safety Population (Section 4.4.4). Ad hoc analyses may be pursued after data collection.

4.9.5 Biomarker Analysis

Biomarker data will be summarized with descriptive statistics by treatment arm using the Safety Population (Section4.4.4). Ad hoc analyses may be pursued after data collection.

4.9.6 Pharmacokinetic Analysis

Pharmacokinetic analyses will be limited to descriptive statistics conducted using the JS001 Treated Subjects. Individual and average concentration-collect time curve will be plotted.

4.10 Interim Analysis

An iDMC will be set up to evaluate safety data on an ongoing basis, as well as the efficacy data from the planned interim efficacy analyses. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an independent party. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

4.10.1 IRC-Assessed PFS

One interim efficacy analysis of PFS was planned to be conducted when approximately 130 PFS events in the ITT population had been observed. This was expected to occur approximately 18 months after the first patient was randomized, although the exact timing of the interim analysis depended on the actual occurrence of PFS events.

The final analysis of PFS was planned to be conducted when approximately 200 PFS events in the ITT population have been observed. This was expected to occur approximately 25

months after the first patient was randomized, while the exact timing of the final analysis will depend on the actual occurrence of PFS events.

To control the type I error for PFS analyses at a two-sided significance level of 0.05, the stopping boundaries for the PFS interim and final analyses were computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundary as shown in the following table:

Timing and Stopping Boundary of PFS Analyses

Type of Analysis	Timing Since FSI (month)	Planned Information Fraction (Event #)	Stopping Boundary (Two-Sided p-Value)
PFS interim analysis	18	65% (130)	0.011
PFS final analysis	25	100% (200)	0.047

FSI = First subject in; PFS = progression-free survival; HR = hazard ratio.

The planned interim analysis was performed with the data cutoff date of 30 May 2020, when 128 PFS events, as assessed by IRC per RECIST 1.1, had been observed in the ITT population. The PFS result generated at the interim analysis was highly statistically significant and was treated as definitive. The final PFS analysis will be conducted 18 months after the last patient was randomized, when it is estimated that approximately 150 IRC-assessed PFS events will be observed in the ITT population. The final PFS analysis will be performed for the descriptive purposes only.

4.10.2 OS

Two interim analyses of OS were planned at the interim and final analyses of PFS for the descriptive purpose only, where it was expected to observe approximately 49 and 74 deaths respectively. The final analysis of OS will be performed when approximately 130 deaths have been observed in the ITT population.

4.11 Determination of Sample Size

The sample size calculation is based on the primary endpoint PFS. Patients will be randomized in a 1:1 ratio. A total of 280 patients (140 per arm) are needed to observe 200 PFS events at approximately 25 months after the first patient is randomized in order to detect the PFS improvement of HR=0.67 with 80% power at a 2-sided significance level of 0.05; one interim analysis is planned when approximately 130 PFS events are observed.

The calculation of the sample size is based on the following assumptions:

- PFS is exponentially distributed
- The median PFS is 7 months for the standard chemotherapy
- The interim and final analyses of PFS use the Lan DeMets alpha spending function to approximate the O'Brien Fleming boundary
- The recruitment of 280 patients will take place over 14 months,

- The dropout rate is 5% over 12 months for PFS.

4.12 Changes in the Conduct of the Study or Planned Analysis

4.12.1 Changes Made in SAP v2.0

The following shows the changes made in the SAP v2.0 compared to the SAP v1.0.

#	**SAP v1.0**	**SAP v2.0**
#1	Section 1 INTRODUCTION This SAP is based upon the following study documents: • Study Protocol, Version 5.0 (Aug 18, 2020)	Section 1 INTRODUCTION This SAP is based upon the following study documents: • Study Protocol, Version 6.0 (12, 2020)
#2	Section 3.1 Overall Study Design and Plan … Crossover will not be permitted as part of this study. Tumor evaluation scans will be performed at screening (as baseline) then every 6 weeks in the first 12 months then every 9 weeks thereafter until objective disease progression. …	Section 3.1 Overall Study Design and Plan … ~~Crossover will not be permitted as part of this study.~~ Tumor evaluation scans will be performed at screening (as baseline) then every 6 weeks in the first 12 months then every 9 weeks thereafter until objective disease progression. …
#3	Section 3.1 Overall Study Design and Plan	Section 3.1 Overall Study Design and Plan <the following new paragraph is added> This is a double blinded and one interim efficacy analysis of PFS is planned and pre-defined stopping boundary is set for two-sided p-value. The iDMC will provide the recommendation as to whether to unblind the study or not according to the data of interim analysis and the iDMC charter if the stopping boundary were met. If the Sponsor accepted the recommendation and unblind the study, JS001 will be provided to the patients who were randomized to arm

#	SAP v1.0	SAP v2.0
		A and still on JS001 treatment until the treatment discontinuation criteria are met according to protocol, the placebo treatment will be terminated for the patients who were randomized to arm B. After the study is unblinded, the tumor evaluation, survival follow-up, safety information, and so on information collection should be performed as required by the protocol.
#4	4.3.1 Disposition of Patients	4.3.1 Disposition of Patients <the following new table is added> • A summary of follow-up time (months), which is defined as the time from randomization to a specified event (death, end of the study or the data cut-off for the analysis, whichever occurs first), by treatment arm and overall, using the ITT population. The study follow-up time (months) is calculated as (event date - randomization date + 1) / 30.4375
#5	4.4.3 Per-Protocol Analysis Set (PPS) The Per-Protocol Analysis Set (PPS) will include all ITT patients who do not have any major protocol violations which have significant impact on the primary outcome measures and have valid baseline and primary outcome measures. Major protocol violations will be defined and inclusion of subjects in the PPS population will be finalized prior to study unbinding. Patients will be analyzed according to the study arm to which they are randomized. The PPS population will be used for some secondary/exploratory analysis as well	4.4.3 Per-Protocol Analysis Set (PPS) The Per-Protocol Analysis Set (PPS) will include all ITT patients who do not have any major protocol violations which may have ~~significant~~ potential impact on the ~~primary outcome measures and have valid baseline and primary outcome measures~~ key efficacy or safety endpoints. Major protocol violations will be defined and inclusion of subjects in the PPS population will be finalized prior to study unbinding. Patients will be analyzed according to the study arm to which they are randomized. The PPS population will be used for some

#	SAP v1.0	SAP v2.0
	as sensitivity analysis of the primary efficacy endpoints.	secondary/exploratory analysis as well as sensitivity analysis of the primary efficacy endpoints.
#6	4.5 Demographic and Other Baseline Characteristics … • A summary of medical history by treatment arm, system organ class, and preferred term, coded by Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher	4.5 Demographic and Other Baseline Characteristics … • A summary of medical history by treatment arm, system organ class, and preferred term, coded by Medical Dictionary for Regulatory Activities (MedDRA) version 23.0
#7	4.5.2 Previous Systemic Therapy … The systemic therapies will be coded using the MedDRA with version 20.0 or higher.	4.5.2 Previous Systemic Therapy … The systemic therapies will be coded using the WHODrug Dictionary.
#8	4.5.5 Previous and Concomitant Medication … The medications will be coded using the World Health Organization-Drug Dictionary Enhanced (WHO-DDE) version March 2019 or later.	4.5.5 Previous and Concomitant Medication … The medications will be coded using the WHODrug Global Dictionary ~~Enhanced (WHO-DDE)~~ version ~~March 2019 or later~~ Mar 2020 B3.
#9	4.5.6 Previous and Concomitant Surgery … The surgeries will be coded using the Medical Dictionary for Regulatory Activities with version 20.0 or higher.	4.5.6 Previous and Concomitant Surgery … The surgeries will be coded using the ~~Medical Dictionary for Regulatory Activities with~~ MedDRA version 23.0 ~~or higher~~.
#10	4.5.7 Concomitant Procedure The concomitant procedure will be coded using the Medical Dictionary for Regulatory Activities with version 20.0 or higher.	4.5.7 Concomitant Procedure The concomitant procedure will be coded using the ~~Medical Dictionary for Regulatory Activities with~~ MedDRA version 23.0 ~~or higher~~.
#11	4.5.8 Post Anti-Cancer Therapy Post anti-cancer therapy will be coded using the World Health Organization-	4.5.8 Post Anti-Cancer Therapy Post anti-cancer therapy will be coded using the ~~World Health Organization-~~

#	SAP v1.0	SAP v2.0
	Drug Dictionary Enhanced (WHO-DDE) version March 2019 or later.	~~Drug~~ WHODrug Global Dictionary ~~Enhanced (WHO-DDE)~~ version ~~March 2019 or later~~ Mar 2020 B3.
#12	4.6 Extent of Exposure The duration of exposure is defined as the duration from the first dosing date to the last dosing date of JS001/placebo at the end of treatment. Duration of exposure (in days) will be calculated as: the last dosing date at the end of treatment – the first dosing date + 1	4.6 Extent of Exposure The duration of exposure is defined as the duration from the first dosing date to the last dosing date of JS001/placebo and chemotherapy (gemcitabine or cisplatin) at the end of treatment. Duration of exposure (in weeks) will be calculated as: (the last dosing date at the end of treatment – the first dosing date + 21) / 7
#13	4.6 Extent of Exposure … A summary of the number of cycles received (number and proportion of patients), actual duration of treatment, actual cumulative total dose received per patient (mg), dose intensity, and relative dose intensity and weeks of exposure for chemotherapy will be provided by treatment arm, using the Safety Population.	4.6 Extent of Exposure … A summary of the number of cycles received (number and proportion of patients), actual duration of treatment, actual cumulative total dose received per patient (mg), dose intensity, and relative dose intensity, weeks and number of cycles for chemotherapy will be provided by treatment arm, using the Safety Population.
#14	4.7.1.4 Examination of Subgroups The primary efficacy endpoint of investigator-assessed PFS according to RECIST v1.1 will be analyzed including but not limited to following subgroups: • Age: ⩽50 vs >50 • Sex: Male and Female • Race: Asian and Others • Baseline ECOG status: 0 and 1 • Disease stage (recurrent versus metastatic) • EBV virus copy number • Baseline PD-1 expression status: PD-1 will be categorized to <1% vs. >= 1%, <5% vs. >= 5%, and <10% vs. >= 10%.	4.7.1.4 Examination of Subgroups The primary efficacy endpoint of investigator-assessed PFS according to RECIST v1.1 will be analyzed including but not limited to following subgroups: • Age: <=50 versus >50 • Sex: Male versus Female ~~• Race: Asian and Others~~ • Baseline ECOG status per CRF: 0 versus 1 • Baseline ECOG status per IWRS: 0 versus 1 • Disease stage per CRF (recurrent versus metastatic) • Disease stage per IWRS (recurrent versus metastatic)

#	SAP v1.0	SAP v2.0
		• EBV virus copy number: <=500 versus >500; <=2000 versus >2000 • Baseline PD-1 expression status: PD-1 will be categorized to <=5% vs. > 5%, and <=10% vs. > 10%.
#15	4.7.2 Primary Efficacy Endpoint – IRC-Assessed PFS … For patients who do not experience disease progression but have started any new anti-tumor therapy, PFS will be censored at the time of the last tumor assessment before the new therapy. For patients who have two consecutive missing tumor assessments, PFS will be censored at the time of the last available tumor assessment before the missing. Due to COVID-19 pandemic, for patients who have two consecutive missing tumor assessments due to COVID-19, in the circumstance if subsequent tumor assessment becomes available and not disease progression, the tumor assessment will be used in the PFS analysis and if the subsequent tumor assessment is disease progression, PFS will still be censored at the time of the last available tumor assessment before the missing.	4.7.2 Primary Efficacy Endpoint – IRC-Assessed PFS … For patients who do not experience disease progression but have started any new anti-tumor therapy, PFS will be censored at the time of the last tumor assessment before the new therapy. For patients who have two or more consecutive missing tumor assessments, PFS will be censored at the time of the last available tumor assessment before the missing~~. Due to~~, or at the date of randomization if there was no post-baseline tumor assessment before the missing. In the COVID-19 pandemic period, for patients who have two or more consecutive missing tumor assessments due to COVID-19, in the circumstance if subsequent tumor assessments become available and there is no immediate disease progression, the subsequent tumor assessments will be used in the PFS analysis and; if the subsequent immediate tumor assessment is disease progression, PFS will still be censored at the last tumor assessment before the missing, or at the date of randomization if there is no post-baseline tumor assessment before the missing.
#16	4.7.3.3 Objective Response Rate (ORR) … The 95% CI for the difference in ORRs between the two treatment arms will be determined using the normal	4.7.3.3 Objective Response Rate (ORR) … The 95% CI for the difference in ORRs between the two treatment arms will be determined using the Mantel-Heanszel method.

#	SAP v1.0	SAP v2.0
	approximation to the binomial distribution.	
	4.7.3.4 Duration of Response (DoR) … If no tumor assessments are performed after the date of the first occurrence of a CR or PR, duration of response will be censored at the date of the first occurrence of a CR or PR plus 1 day.	4.7.3.4 Duration of Response (DoR) … If no tumor assessments are performed after the date of the first occurrence of a CR or PR, duration of response will be censored at the date of the first occurrence of a CR or PR ~~plus 1 day~~.
#17	4.8.1 Adverse Events AEs will be coded using the Medical Dictionary for Regulatory Activities with version 20.0 or higher.	4.8.1 Adverse Events AEs will be coded using the ~~Medical Dictionary for Regulatory Activities with~~ MedDRA version 23.0 ~~or higher~~.
#18	4.8.1 Adverse Events … Following summaries will be provided: • An overview of all TEAEs: the number and percentage of patients with any TEAEs, TEAEs with relationship to study drug, any TEAEs with relationship to chemotherapy, any AEs leading to drug withdrawn, any TEAEs leading to drug interruption, any TEAEs leading to dose reduced, and any TEAEs leading to death, by treatment arm …	4.8.1 Adverse Events … Following summaries will be provided: • An overview of all TEAEs: the number and percentage of patients with any TEAEs, any >= grade 3 TEAE, any treatment-emergent immune-related adverse event (irAE), any treatment emergent adverse events of special interest (AESI), any >= grade 3 treatment-emergent AESI, any SAE, any TEAEs with relationship to study drug, any TEAEs with relationship to gemcitabine, any TEAEs with relationship to cisplatin, any TEAEs leading to drug withdrawn, any TEAEs leading to drug interruption, any TEAEs leading to dose reduced, and any TEAEs leading to death, by treatment arm … • A summary of the number and percentage of patients reporting a TEAE, by treatment arm, maximum severity (grade 1-2, grade 3, grade 4, grade 5, >= grade 3), system organ class, and preferred term … •A summary of the number and percentage of patients reporting treatment-emergent irAE, by treatment

#	SAP v1.0	SAP v2.0
		arm, maximum severity (grade 1-2, grade 3, grade 4, grade 5, >= grade 3), system organ class, and preferred term … • A summary of the number and percentage of patients reporting a study drug related TEAEs, by treatment arm, maximum severity (grade 1-2, grade 3, grade 4, grade 5, >= grade 3), system organ class, and preferred term • A summary of the number and percentage of patients reporting a gemcitabine related TEAE and the number of gemcitabine related TEAEs, by treatment arm, system organ class, and preferred term • A summary of the number and percentage of patients reporting a cisplatin related TEAE and the number of cisplatin related TEAEs, by treatment arm, system organ class, and preferred term
#19	4.8.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events … Following summaries will be provided: • An overview of all SAEs including all SAEs, any study drug related SAE, any SAEs with relationship to chemotherapy, any SAEs leading to drug withdrawn, any SAEs leading to drug interruption, any SAEs leading to dose reduced, and any SAEs leading to death, by treatment arm	4.8.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events … Following summaries will be provided: ~~• An overview of all SAEs including all SAEs, any study drug related SAE, any SAEs with relationship to chemotherapy, any SAEs leading to drug withdrawn, any SAEs leading to drug interruption, any SAEs leading to dose reduced, and any SAEs leading to death, by treatment arm~~
#20	4.8.3 Vital Signs and Weight … If repeat measurements are taken at a particular time point, the first valid measurement will be used in the summaries.	4.8.3 Vital Signs and Weight … If repeat measurements are taken at a particular time point, the last valid measurement will be used in the summaries.
#21	4.9.1 Sensitivity Analyses for IRC-Assessed PFS …	4.9.1 Sensitivity Analyses for IRC-Assessed PFS …

#	SAP v1.0	SAP v2.0
	• The analysis using the methods outlined for the primary analysis. Regardless patients with disease progression or death being documented after missing two consecutive tumor assessments due to COVID-19, PFS will be censored at the last tumor assessment before the missing.	• The analysis using the methods outlined for the primary analysis. Regardless patients with disease progression or death being documented after missing two consecutive tumor assessments due to COVID-19, PFS will be censored at the last tumor assessment before the missing, or at the randomization date if there was no post-baseline tumor assessment before the missing.
#22	7 APPENDIX B GRADING CRITERIA FOR CLINICAL LABORATORY TESTS	6.2 APPENDIX B GRADING CRITERIA FOR CLINICAL LABORATORY TESTS Global updates to CTCAE grading criteria to 5.0

4.12.2 Changes Made in SAP v3.0

The following changes to the analyses specified in the protocol have been made in the SAP v3.0

- Per FDA's request received in April, 2020 during the IND application in the US, overall Type I error rate has been controlled for both the primary efficacy endpoint and the key secondary efficacy endpoints (IRC-assessed ORR and OS), instead of the primary efficacy endpoint only, as the interim analysis of primary efficacy endpoint IRC-assessed PFS has crossed the pre-specified O'Brien-Fleming boundary.
- Final PFS analysis will be conducted when approximately 18 months after the last patient was randomized, instead of 200 PFS events have been observed.

The following shows the changes made in the SAP v3.0 compared to the SAP v2.0.

#	SAP v2.0	SAP v3.0
#1	Section 1 INTRODUCTION This SAP is based upon the following study documents: … • Electronic Case Report Form (eCRF), Version 7.0 (Jun 29, 2020)	Section 1 INTRODUCTION This SAP is based upon the following study documents: … • Electronic Case Report Form (eCRF), Version 9.0 (Sep 11, 2020)
#2	4.5.1 Nasopharyngeal Carcinoma Diagnosis …	4.5.1 Nasopharyngeal Carcinoma Diagnosis …

#	SAP v2.0	SAP v3.0
		<the following new paragraph is added> For the nasopharyngeal carcinoma diagnosis, the histology information recorded in the CRF of "Other" and "Unknown" is diverse therefore the data are manually reviewed and further categorized into "Nasopharyngeal carcinoma, unclassified", "Non-keratinizing squamous cell carcinoma, undifferentiated", "Non-keratinizing carcinoma, unclassified", or "Other (please see Section 6.3 Appendix C).
#3	4.6 Extent of Exposure … The actual cumulative total dose of received (mg) is defined as the summation of all actual total dose administrated from the first dosing date to the last dosing date at the end of treatment. … where the planned cumulative total dose of received will be calculated according to the Q3W schedule (i.e. every 3 weeks) using the duration of exposure:	4.6 Extent of Exposure … The actual cumulative total dose of JS001 received (mg) is defined as the summation of all actual total dose administrated from the first dosing date to the last dosing date at the end of treatment. For cisplatin and gemcitabine, the actual cumulative total dose received will be calculated cumulatively based on the data from CRF Drug Administration (Cisplatin/Gemcitabine): "Actual total dose administered". … where the planned cumulative total dose of JS001 received will be calculated according to the Q3W schedule (i.e. every 3 weeks) using the duration of exposure: … For cisplatin and gemcitabine, the planned cumulative total dose received will be calculated cumulatively based on the data from CRF Drug Administration(Cisplatin/Gemcitabine): "Planned total dose administered".
#4	4.7.1 Analysis and Data Handling	4.7.1 Analysis and Data Handling

#	SAP v2.0	SAP v3.0
	…	… <the following new paragraph is added> The study has crossed the O'Brien-Fleming boundary for the planned interim analysis of IRC-assessed PFS, with a data cutoff date of 30 May 2020, when 128 IRC-assessed PFS events had been observed in the ITT population. The key secondary efficacy endpoints, including IRC-assessed objective response rate (ORR) and overall survival (OS), were to be tested hierarchically under a two-sided alpha level of 0.05. ORR was formally tested and reached its statistical significance at the interim analysis of PFS. OS will then be formally tested when 130 deaths are observed in the ITT population.
#5	4.7.2 Primary Efficacy Endpoint – IRC-Assessed PFS …	4.7.2 Primary Efficacy Endpoint – IRC-Assessed PFS … <the following new paragraph is added> If the day of death is missing, it would be imputed with day 15.
#6	4.7.3.2 Overall Survival (OS) …	4.7.3.2 Overall Survival (OS) … <the following new paragraph is added> If the day of death is missing, it would be imputed with day 15.
#7	4.7.3.3 Objective Response Rate (ORR) …	4.7.3.3 Objective Response Rate (ORR) … <the following new paragraph is added> Any tumor assessment, either by the IRC or the investigator, after the first

#	SAP v2.0	SAP v3.0
		PD or the new anti-cancer therapy will not be used to determine the best overall response evaluation.
#8	4.8.1 Adverse Events …	4.8.1 Adverse Events … <the following new paragraph is added> The incidence of some AEs, which should have been summarized under the same preferred term, could be underestimated because they were coded to different preferred terms due to different reported terms. Aside from the MedDRA dictionary, additional aggregation rule are applied to the following AEs: Leukopenia, Neutropenia, Thrombocytopenia, Lymphopenia, Hypokalemia, Fatigue, Rash, Musculoskeletal pain, Cough, Diarrhea, Pneumonia, Neuropathy peripheral, Upper respiratory tract infection, Abdominal pain, Arrhythmia, Oedema, Proteinuria, Hypertension, Blood bilirubin increased, Insomnia (please see Section 6.4 Appendix D).
#9	4.8.5 Laboratory Evaluation …	4.8.5 Laboratory Evaluation … <the following new paragraph is added> The toxicity grade and abnormality worsened from the baseline will be summarized according to NCI-CTCAE version 5.0 (please see Section 6.2 Appendix B).
#10	4.9.2 PFS, ORR, DoR, and DCR per Immune-Related RECIST Analyses using irRECIST for PFS, ORR, DoR and DCR as determined by the IRC and investigator will be conducted for JS001 treated patients only. The applicable methods	4.9.2 PFS, ORR, DoR, and DCR per Immune-Related RECIST Analyses using irRECIST for PFS, ORR, DoR and DCR as determined by the IRC and investigator will be conducted ~~JS001 treated patients only~~. The applicable methods outlined for

#	SAP v2.0	SAP v3.0
	outlined for PFS and ORR will be used for these analyses.	PFS and ORR will be used for these analyses.
#11		<the following new section is added> 4.9.6 Pharmacokinetic Analysis Pharmacokinetic analyses will be limited to descriptive statistics conducted using the Safety Population (Section 4.4.4). Individual and average concentration-collect time curve will be plotted.
#12	4.10 Interim Analysis … One interim efficacy analysis of PFS is planned when approximately 130 PFS events in the ITT population have been observed. This is expected to occur approximately 18 months after the first patient is randomized, while the exact timing of the interim analysis will depend on the actual occurrence of PFS events. The final analysis of PFS will be conducted when approximately 200 PFS events in the ITT population have been observed. This is expected to occur approximately 25 months after the first patient is randomized, while the exact timing of the final analysis will depend on the actual occurrence of PFS events. To control the type I error for PFS analyses at a two-sided significance level of 0.05, the stopping boundaries for PFS interim and final analyses have been computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundary as shown in the following table:	4.10 Interim Analysis … 4.10.1 IRC-Assessed PFS One interim efficacy analysis of PFS was planned to be conducted when approximately 130 PFS events in the ITT population had been observed. This was expected to occur approximately 18 months after the first patient was randomized, although the exact timing of the interim analysis depended on the actual occurrence of PFS events. The final analysis of PFS was planned to be conducted when approximately 200 PFS events in the ITT population have been observed. This was expected to occur approximately 25 months after the first patient was randomized, while the exact timing of the final analysis will depend on the actual occurrence of PFS events. To control the type I error for PFS analyses at a two-sided significance level of 0.05, the stopping boundaries for the PFS interim and final analyses were computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundary as shown in the following table:
#13	4.10 Interim Analysis	4.10 Interim Analysis

#	SAP v2.0	SAP v3.0
	…	… 4.10.1 IRC-Assessed PFS <the following new paragraph is added> The planned interim analysis was performed with the data cutoff date of 30 May 2020, when 128 PFS events, as assessed by IRC per RECIST 1.1, had been observed in the ITT population. The PFS result generated at the interim analysis was highly statistically significant and was treated as definitive. The final PFS analysis will be conducted 18 months after the last patient was randomized, when it is estimated that approximately 150 IRC-assessed PFS events will be observed in the ITT population. The final PFS analysis will be performed for the descriptive purposes only. <the following new sections are added> 4.10.2 OS Two interim analyses of OS were planned at the interim and final analyses of PFS for the descriptive purpose only, where it was expected to observe approximately 49 and 74 deaths respectively. The final analysis of OS will be performed when approximately 130 deaths have been observed in the ITT population.
#14		<the following new sections are added> 6.3 Appendix C: Nasopharyngeal Carcinoma Diagnosis 6.4 Appendix D

5 REFERENCES

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6 APPENDIX

6.1 Appendix A: Patient-Reported Outcomes Scoring Conversion Rule

The principle for scoring

1. Estimate the average of the items that contribute to the scale; this is the raw score calculate by

$$RawScore = RS = \frac{I_1 + I_2 + \cdots + I_n}{n}$$

where $I_1, I_2, \ldots, I_n$ are items in the scale.

2. Apply the linear transformation to 0-100 to obtain the score S,
   - Functional scales:

$$S = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

   - Symptom scales / items:

$$S = \left\{\frac{(RS - 1)}{range}\right\} \times 100$$

   - Global health status / QoL:

$$S = \left\{\frac{(RS - 1)}{range}\right\} \times 100$$

   where $range$ is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving $range = 3$. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with $range = 6$. The QLQ-H&N35 has been designed so that all items in any scale take the same range of values as well, i.e., the range of RS equals the range of the item values. Most items are scored 1 to 4, giving $range = 3$. The exceptions are the items contributing to Pain killers, Nutritional supplements, Feeding tube, Weight loss, and Weight gain, which have $range = 1$.

Table A1. Scoring the QLQ-C30

	Scale	Number of items	Item range	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL	QL2	2	6	29, 30	
Functional scales					
Physical functioning	PF2	5	3	1 to 5	F
Role functioning	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F

Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

Table A2. Scoring the QLQ-H&N35

Scale name	Scale	Number of items	Item range	QLQ-H&N35 Item numbers
Symptom scales / items				
Pain	HNPA	4	3	1 – 4 (CRF 31 – 34)
Swallowing	HNSW	4	3	5 – 8 (CRF 35 – 38)
Senses problems	HNSE	2	3	13,14 (CRF 43 – 44)
Speech problems	HNSP	3	3	16,23,24 (CRF 46, 53, 54)
Trouble with social eating	HNSO	4	3	19 – 22 (CRF 49 – 52)
Trouble with social contact	HNSC	5	3	18,25 – 28 (CRF 48, 55 – 58)
Less sexuality	HNSX	2	3	29,30 (CRF 59, 60)
Teeth	HNTE	1	3	9 (CRF 39)
Opening mouth	HNOM	1	3	10 (CRF 40)
Dry mouth	HNDR	1	3	11 (CRF 41)
Sticky saliva	HNSS	1	3	12 (CRF 42)
Coughing	HNCO	1	3	15 (CRF 45)
Felt ill	HNFI	1	3	17 (CRF 47)
Pain killers	HNPK	1	1	31 (CRF 61)

Nutritional supplements	HNNU	1	1	32 (CRF 62)
Feeding tube	HNFE	1	1	33 (CRF 63)
Weight loss	HNWL	1	1	34 (CRF 64)
Weight gain	HNWG	1	1	35 (CRF 65)

6.2 Appendix B: Grading Criteria For Clinical Laboratory Tests

Hematology Tests		Criteria			
Test	**Direction**	**1**	**2**	**3**	**4**
Hemoglobin (g/L)	Increase	Increase in >0 - 20 g/L above ULN	Increase in >20 - 40 g/dL above ULN	Increase in >40 g/L above ULN	NA
Hemoglobin (g/L)	Decrease	≥100 - <LLN	≥80 - <100.0	<80	NA
Neutrophils (10^9/L)	Decrease	≥1.5 - <LLN	≥1.0 - <1.5	≥0.5 - <1.0	<0.5
Platelets (10^9/L)	Decrease	≥75.0 - <LLN	≥50.0 - <75.0	≥25.0 - <50.0	<25.0
Total WBC count (10^9/L)	Decrease	≥3.0 - <LLN	≥2.0 - <3.0	≥1.0 - <2.0	<1.0
Lymphocytes (10^9/L)	Increase	NA	>4 - ≤20	>20	NA
Lymphocytes (10^9/L)	Decrease	≥0.8 - <LLN	≥0.5 - <0.8	≥0.2 - <0.5	<0.2

Chemistry Tests		Criteria			
Test	**Direction**	**1**	**2**	**3**	**4**
ALT	Increase	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
AST	Increase	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Albumin (g/L)	Decrease	≥30 - <LLN	≥20 - <30	<20	
Alkaline Phosphatase	Increase	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Bilirubin (total)	Increase	>ULN - 1.5 x ULN if baseline	>1.5 - 3.0 x ULN if baseline	>3.0 - 10.0 x ULN if baseline	>10.0 x ULN if baseline was

		was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	was normal; >1.5 - 3.0 x baseline if baseline was abnormal	was normal; >3.0 - 10.0 x baseline if baseline was abnormal	normal; >10.0 x baseline if baseline was abnormal
Calcium (mmol/L)	Increase	>ULN - ≤2.9	>2.9 - ≤3.1	>3.1 - ≤3.4	>3.4
Calcium (mmol/L)	Decrease	>=2.0 - <LLN	>=1.75 - <2.0	>=1.5 - <1.75	<1.5
Creatinine	Increase	>ULN - ≤1.5 xULN	>1.5 xULN - ≤3.0 xULN	>3.0 xULN - ≤6.0 xULN	>6.0 xULN
Potassium (mmol/L)	Increase	>ULN - ≤5.5	>5.5 - ≤6.0	>6.0 - ≤7.0	>7.0
Potassium (mmol/L)	Decrease	≥3.0 - <LLN		≥2.5 - <3.0	<2.5
Sodium (mmol/L)	Increase	>ULN - ≤150	>150 - ≤155	>155 - ≤160	>160
Sodium (mmol/L)	Decrease	≥130 - <LLN	≥125 - <130	≥120 - <125	<120
Glucose (mmol/L)	Decrease	≥ 3 - <LLN	≥ 2.2 - <3	≥ 1.7 - <2.2	<1.7

6.3 Appendix C: Nasopharyngeal Carcinoma Diagnosis

The "Other" or "Unknown" histology type recorded in the CRF are re-mapped according to the following table:

Histology type	If other, please specify	Histology type-New
Other	Metastatic nasopharyngeal carcinoma[center Histology report]	Nasopharyngeal carcinoma,unclassified
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	undifferentiated,non-keratinizing carcinoma(local Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Malignant tumor(center Histology report),undifferentiated Non-keratinizing carcinoma(local Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	undifferentiated,non-keratinizing carcinoma(local Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified

Histology type	If other, please specify	Histology type-New
Other	undifferentiated Non-keratinizing carcinoma(local Histology report), diagnos is uncler(center Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	undifferentiated Non-keratinizing carcinoma(local Histology report),No tumor is found(center Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	undifferentiated,non-keratinizing carcinoma(local Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	undifferentiated Non-keratinizing carcinoma(local Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	undifferentiated Non-keratinizing carcinoma(local Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	poorly differentiated carcinoma(local Histology report），diagnos is uncler(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	undifferentiated Non-keratinizing carcinoma(local Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Malignant tumor[Center Histology report],undifferentiated,non-keratinizing carcinoma(local Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	undifferentiated Non-keratinizing carcinoma(local Histology report)(local Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	undifferentiated,non-keratinizing carcinoma(local Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Poorly differentiated squamous cell carcinoma(local Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Malignant tumor[Center Histology report],undifferentiated,non-keratinizing carcinoma(local Histology report)	Non-keratinizing squamous cell carcinoma, undifferentiated

Histology type	If other, please specify	Histology type-New
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma[center Histology report]	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	nasopharyngeal carcinoma(center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Non-keratinizing squamous cell carcinoma, undifferentiated(local report)	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Metastatic nasopharyngeal carcinoma (Central Pathology Report)	Nasopharyngeal carcinoma,unclassified
Other	Malignant tumor,important differential dignoses include nasopharyngeal carcinoma and neuroendocrine carcinoma.More IHC tests are essential for further diagnosis	Nasopharyngeal carcinoma,unclassified
Other	metastatic lymphoepithelial carcinoma	Nasopharyngeal carcinoma,unclassified
Other	Metastasis of nasopharyngeal carcinoma	Nasopharyngeal carcinoma,unclassified
Other	Non-keratinzing squamous cell carcinoma,undifferentiated subtype	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Non-keratinizing squamous cell carcinoma, undifferentiated subtype	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Non-keratinizing squamous cell carcinoma, undifferentiated subtype	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Non-keratinizing squamous cell carcinoma, undifferentiated subtype	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Non-keratinizing squamous cell carcinoma, undifferentiated subtype	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Non-keratinizing squamous cell carcinoma,undifferentiated subtype is considered(center Histology report).	Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Metastatic nasopharyngeal carcinoma (center Histology report)	Nasopharyngeal carcinoma,unclassified

Histology type	If other, please specify	Histology type-New
Other	squamous carcinoma	Nasopharyngeal carcinoma,unclassified
Other	Non - keratinizing carcinoma	Non-keratinizing carcinoma,unclassified
Other	Non-keratinizing carcinoma	Non-keratinizing carcinoma,unclassified
Other	Non-keratinizing carcinoma	Non-keratinizing carcinoma,unclassified
Other	Non-keratinizing carcinoma	Non-keratinizing carcinoma,unclassified
Other	Non-keratinizing carcinoma	Non-keratinizing carcinoma,unclassified
Other	Non-keratinizing carcinoma	Non-keratinizing carcinoma,unclassified
Other	Non-keratinizing carcinoma	Non-keratinizing carcinoma,unclassified
Other	Non-keratinizing carcinoma	Non-keratinizing carcinoma,unclassified
Other	Non-keratinizing carcinoma	Non-keratinizing carcinoma,unclassified
Other	Non-keratinizing carcinoma	Non-keratinizing carcinoma,unclassified
Other	Non-keratinizing carcinoma	Non-keratinizing carcinoma,unclassified
Other	Nasopharyngeal carcinoma	Nasopharyngeal carcinoma,unclassified
Other	Lymphoepithelial carcinoma	Nasopharyngeal carcinoma,unclassified
Other	Metastatic Lymphoepithelial carcinoma	Nasopharyngeal carcinoma,unclassified
Other	squamous cell carcinoma	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma (center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma (center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Metastatic nasopharyngeal carcinoma (center Histology report)	Nasopharyngeal carcinoma,unclassified
Other	Poorly differentiated squamous cell carcinoma（local pathological report）	Nasopharyngeal carcinoma,unclassified
Other	nasopharynx（Non-keratinizing cell carcinoma, undifferentiated）	Non-keratinizing squamous cell carcinoma, undifferentiated
Unknown		Non-keratinizing squamous cell carcinoma, undifferentiated
Other	Malignant tumor, metastatic poorly differentiated carcinoma（site pathological report）	Nasopharyngeal carcinoma,unclassified

Histology type	If other, please specify	Histology type-New
Other	left parotid sarcoma, pleomorphic rhabdomyosarcoma（site pathological report）	Other
Other	Nasopharyngeal carcinoma (central pathology report)	Nasopharyngeal carcinoma,unclassified
Other	Nasopharyngeal carcinoma (central pathology report)	Nasopharyngeal carcinoma,unclassified
Other	Lymphoepitheliomatous nasopharyngeal carcinoma	Nasopharyngeal carcinoma,unclassified
Other	Nasopharyngeal carcinoma	Nasopharyngeal carcinoma,unclassified
Other	Nasopharyngeal carcinoma with lymphoepithelioma-like carcinoma	Nasopharyngeal carcinoma,unclassified
Other	Nonkeratinising Nasopharyngeal Carcinoma	Non-keratinizing carcinoma,unclassified
Other	Undifferentiated Carcinoma	Nasopharyngeal carcinoma,unclassified

6.4 Appendix D

Previous AE PT	Aggregated AE PT	Aggregated AE SOC
White blood cell count decreased	Leukopenia	Blood and lymphatic system disorders
Leukopenia	Leukopenia	Blood and lymphatic system disorders
Neutrophil count decreased	Neutropenia	Blood and lymphatic system disorders
Febrile neutropenia	Neutropenia	Blood and lymphatic system disorders
Granulocytopenia	Neutropenia	Blood and lymphatic system disorders
Neutropenia	Neutropenia	Blood and lymphatic system disorders
Platelet count decreased	Thrombocytopenia	Blood and lymphatic system disorders
Thrombocytopenia	Thrombocytopenia	Blood and lymphatic system disorders
Lymphocyte count decreased	Lymphopenia	Blood and lymphatic system disorders
T-lymphocyte count decreased	Lymphopenia	Blood and lymphatic system disorders
Lymphopenia	Lymphopenia	Blood and lymphatic system disorders
Blood potassium decreased	Hypokalaemia	Metabolism and nutrition disorders
Hypokalaemia	Hypokalaemia	Metabolism and nutrition disorders
Malaise	Fatigue	General disorders and administration site conditions
Asthenia	Fatigue	General disorders and administration site conditions
Fatigue	Fatigue	General disorders and administration site conditions
Catheter site rash	Rash	Skin and subcutaneous tissue disorders
Rash maculo-papular	Rash	Skin and subcutaneous tissue disorders
Erythema	Rash	Skin and subcutaneous tissue disorders
Drug eruption	Rash	Skin and subcutaneous tissue disorders
Papule	Rash	Skin and subcutaneous tissue disorders
Rash pruritic	Rash	Skin and subcutaneous tissue disorders
Rash	Rash	Skin and subcutaneous tissue disorders
Back pain	Musculoskeletal pain	Musculoskeletal and connective tissue disorders

Previous AE PT	Aggregated AE PT	Aggregated AE SOC
Neck pain	Musculoskeletal pain	Musculoskeletal and connective tissue disorders
Pain in extremity	Musculoskeletal pain	Musculoskeletal and connective tissue disorders
Bone pain	Musculoskeletal pain	Musculoskeletal and connective tissue disorders
Pain in jaw	Musculoskeletal pain	Musculoskeletal and connective tissue disorders
Musculoskeletal chest pain	Musculoskeletal pain	Musculoskeletal and connective tissue disorders
Myalgia	Musculoskeletal pain	Musculoskeletal and connective tissue disorders
Musculoskeletal pain	Musculoskeletal pain	Musculoskeletal and connective tissue disorders
Chest pain	Musculoskeletal pain	Musculoskeletal and connective tissue disorders
Non-cardiac chest pain	Musculoskeletal pain	Musculoskeletal and connective tissue disorders
Productive cough	Cough	Respiratory, thoracic and mediastinal disorders
Cough	Cough	Respiratory, thoracic and mediastinal disorders
Diarrhoea	Diarrhoea	Gastrointestinal disorders
Gastroenteritis	Diarrhoea	Gastrointestinal disorders
Pneumonia	Pneumonia	Infections and infestations
Pneumonia aspiration	Pneumonia	Infections and infestations
Hypoaesthesia	Neuropathy peripheral	Nervous system disorders
Neuropathy peripheral	Neuropathy peripheral	Nervous system disorders
Paraesthesia	Neuropathy peripheral	Nervous system disorders
Peripheral sensory neuropathy	Neuropathy peripheral	Nervous system disorders
Peroneal nerve palsy	Neuropathy peripheral	Nervous system disorders
Rhinitis	Upper respiratory tract infection	Infections and infestations
Sinusitis	Upper respiratory tract infection	Infections and infestations
Acute sinusitis	Upper respiratory tract infection	Infections and infestations
Upper respiratory tract infection	Upper respiratory tract infection	Infections and infestations
Nasopharyngitis	Upper respiratory tract infection	Infections and infestations
Bronchitis	Upper respiratory tract infection	Infections and infestations
Laryngitis	Upper respiratory tract infection	Infections and infestations

Previous AE PT	Aggregated AE PT	Aggregated AE SOC
Pharyngitis	Upper respiratory tract infection	Infections and infestations
Respiratory tract infection	Upper respiratory tract infection	Infections and infestations
Abdominal pain	Abdominal pain	Gastrointestinal disorders
Abdominal discomfort	Abdominal pain	Gastrointestinal disorders
Abdominal pain upper	Abdominal pain	Gastrointestinal disorders
Abdominal pain lower	Abdominal pain	Gastrointestinal disorders
Sinus arrhythmia	Arrhythmia	Cardiac disorders
Sinus bradycardia	Arrhythmia	Cardiac disorders
Tachycardia	Arrhythmia	Cardiac disorders
Tachycardia paroxysmal	Arrhythmia	Cardiac disorders
Peripheral swelling	Oedema	General disorders and administration site conditions
Oedema	Oedema	General disorders and administration site conditions
Oedema peripheral	Oedema	General disorders and administration site conditions
Face oedema	Oedema	General disorders and administration site conditions
Swelling face	Oedema	General disorders and administration site conditions
Eyelid oedema	Oedema	General disorders and administration site conditions
Periorbital oedema	Oedema	General disorders and administration site conditions
Generalised oedema	Oedema	General disorders and administration site conditions
Proteinuria	Proteinuria	Renal and urinary disorders
Protein urine present	Proteinuria	Renal and urinary disorders
Blood pressure systolic increased	Hypertension	Vascular disorders
Blood pressure increased	Hypertension	Vascular disorders
Hypertension	Hypertension	Vascular disorders
Hypertensive crisis	Hypertension	Vascular disorders
Blood bilirubin increased	Blood bilirubin increased	Investigations
Blood bilirubin unconjugated increased	Blood bilirubin increased	Investigations
Insomnia	Insomnia	Psychiatric disorders
Initial insomnia	Insomnia	Psychiatric disorders