Drug Clinical Trial Approval Letter No.: 2017L04750

Registration Category 1 of Therapeutic Biological Products

Clinical Study Protocol

A Phase 2 Clinical Study To Evaluate the Efficacy and Safety of KL-A167 Injection in Patients with Recurrent or Metastatic Nasopharyngeal Carcinoma (NPC)

Protocol No.	**:**	**KL167-II-05-CTP**
Version No.	**:**	**V3.0**
Version Date	**:**	**22 Mar, 2021**
Leading Study Site	**:**	**Cancer Hospital Chinese Academy of Medical Sciences**
Principal Investigator	**:**	**SHI Yuankai**
Sponsor	**:**	**Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd**
Principal Leader	**:**	**QING Yan**

Sponsor, Investigator's Statement and Signature Page

(I) Sponsor's Statement

I have read and understood the study protocol. I agree that the study will be conducted in accordance with the protocol, and I will perform all relevant obligations and follow other relevant requirements related to the Sponsor in compliance with the Good Clinical Practice (GCP) and the Declaration of Helsinki. I agree to comply with all the standard operating procedures (SOPs) related to the conduct of this study at the study sites, each participating institution, and Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

Sponsor's Medical Director: WEI Youneng

Signature of the Sponsor's Medical Director: Date: _____DD_____MM_____YYYY

Sponsor's Director: QING Yan

Signature of the Sponsor's Director: Date: _____DD_____MM_____YYYY

(II) Investigator's Statement

I have read and understood the study protocol and agree to conduct this clinical study in accordance with the design and regulations of this protocol. The study will be conducted in accordance with the moral, ethical and scientific principles set forth in the Declaration of Helsinki and GCP. I agree to comply with all the SOPs related to the conduct of this study at the clinical research facility of this hospital and Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

I will ensure that subjects are treated promptly when adverse events (AEs) occur during this study. I understand the requirements for proper reporting of serious adverse events (SAEs), and I will record and report these events as required.

I guarantee that the data will be accurately, completely and timely recorded in the original documents to ensure the quality of the clinical study. I will accept the monitoring and auditing by monitors and auditors dispatched by the sponsor, as well as inspections by drug regulatory authorities.

The information contained herein and any information of protocol addendum is confidential and is the property of Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. I guarantee that the contents of this protocol will not be used in any other clinical studies, and will not be disclosed to any other individuals or groups unrelated to the study without the prior written permission of Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

Clinical Research Facility:_____

Principal Investigator:_____

Investigator's Signature:_____ Date: _____DD_____MM_____YYYY

Compliance Statement

This study will be conducted in compliance with the GCP, ICH-GCP and the following regulations and guidelines applicable to clinical studies:

1) Drug Administration Law of the People's Republic of China (2019)
2) Drug Registration Regulation (2020)
3) Declaration of Helsinki (2013)
4) Technical Guidelines for Clinical Pharmacokinetic Studies on Chemical Drugs (2005)
5) Guidelines for the Management of Bioanalytical Laboratories for Clinical Trials (Trial) (2011)

The principal investigator will ensure that the protocol will not be violated or changed until approved by the sponsor and the EC, except in order to avoid a direct hazard to the subjects.

The protocol, informed consent form (ICF), blank case report form (CRF), drug regulatory authority's permission, filing and certificates of analysis, and subject recruitment advertisement will be submitted to the EC for review and approval. The approval from the EC must be received prior to enrollment of subjects. Any amendment to the protocol must be reviewed and approved by the EC before implementation.

Protocol Synopsis

Study Title	A Phase 2 Clinical Study to Evaluate the Efficacy and Safety of KL-A167 Injection in Patients with Recurrent or Metastatic NPC
Study Objectives	**Primary objective:** To evaluate the objective response rate (ORR) of KL-A167 Injection in patients with recurrent or metastatic NPC, as assessed by the Independent Review Committee using Response Evaluation Criteria in Solid Tumors v1.1 (RECIST 1.1). **Secondary objectives:** 1) To evaluate the investigator-assessed ORR of KL-A167 Injection in patients with recurrent or metastatic NPC as per RECIST V1.1 and irRECIST, respectively; 2) To evaluate progression-free survival (PFS), overall survival (OS), disease control rate (DCR), duration of response (DoR), and time to response (TTR) of KL-A167 Injection in patients with recurrent or metastatic NPC; 3) To evaluate the pharmacokinetics (PK) characteristics of KL-A167 Injection in patients with recurrent or metastatic NPC; 4) To evaluate the safety of KL-A167 Injection in patients with recurrent or metastatic NPC; 5) To evaluate the immunogenicity of KL-A167 Injection in patients with recurrent or metastatic NPC. **Exploratory objective:** To evaluate the correlation between the expression of biomarkers (PD-L1 and sPD-L1) and treatment response.
Investigational Product	KL-A167 Injection, 200 mg (10 mL)/vial; with a tentative shelf life of 3 years; stored in tightly closed containers at 2-8 ℃ and protected from light.
Study Subjects	Patients with recurrent or metastatic nasopharyngeal carcinoma who have failed ≥ 2 lines of chemotherapy
Phase of Development	2
Study Design	This is a single-arm, open-label, multicenter study to evaluate the efficacy and safety of KL-A167 Injection in patients with recurrent or metastatic NPC who have failed ≥ 2 lines of chemotherapy. **Method of Administration** The subjects will receive KL-A167 Injection 900 mg as an intravenous infusion on Day 1 of each cycle (one cycle = 14 days). No more than 30 mL will be infused for the first 30 minutes of each cycle, and the total duration of infusion should not be less than 120 minutes. Dosing will be continued until confirmed progressive disease (PD) or intolerable toxicity or withdrawal of consent (Note: “Confirmed PD” is defined as the PD confirmed as per

	irRECIST and the subject has no further potential to obtain clinical benefit as judged by the investigator).
Sample Size	The assumed ORR of KL-A167 Injection in the treatment of recurrent or metastatic NPC could reach 26%. The investigational product will be considered effective if the lower limit of the 95% confidence interval (CI) for ORR is not less than 15%. Based on the 95% CI of ORR estimated by the Clopper-Pearson method, the drug can be considered effective based on a statistical power of 90% obtained for 139 samples at a level where type 1 error is controlled to two-sided 0.05. A total of approximately 153 subjects will be required considering a dropout rate of 10%.
Inclusion Criteria	Subjects may be entered in the study only if they meet all of the following criteria: 1) Aged ≥ 18 years old, male or female; 2) Subjects with histopathologically confirmed recurrent/metastatic nonkeratinizing differentiated or undifferentiated NPC; 3) Subjects with diseases of clinical stage IVB [Staging System of American Joint Committee on Cancer (AJCC) (8th edition)] who have received first line of platinum-containing combination chemotherapy and second line of monotherapy or failure of combination therapy; 4) Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1; 5) Expected survival ≥ 12 weeks; 6) Subjects with at least one measurable lesion according to RECIST 1.1, and lesions that have been treated with local therapies, such as radiotherapy, cannot be considered as measurable lesions; 7) Tissue or tissue samples must be provided for biomarker analysis. Newly obtained tissues are preferred, and archived paraffin slices are acceptable for patients who do not have newly obtained tissues; 8) Adequate organ and bone marrow function, as defined below: a) Hematology: neutrophil count (NEUT #) ≥ 1.5 × 10^9/L; platelet count (PLT) ≥ 90 × 10^9/L; hemoglobin concentration ≥ 9 g/dL; b) Hepatic function: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN); total bilirubin (TBIL) ≤ 1.5 × ULN; ALT and AST ≤ 5 × ULN for subjects with liver metastases; TBIL ≤ 2 × ULN for subjects with liver metastases or Gilbert's syndrome; c) Renal function: creatinine clearance (CCR) ≥ 50 mL/min; d) Coagulation function: international normalized ratio (INR) ≤ 1.5 and activated partial thromboplastin time (APTT) ≤ 1.5 × ULN; 9) Subjects who have taken chemotherapeutic drugs which should be discontinued for ≥ 4 weeks before the first dose (mitomycin or nitrosoureas should be discontinued for ≥ 6 weeks); received surgery, molecular targeted therapy, traditional Chinese medicine

	therapy with anti-tumor indications, radiotherapy, and anti-tumor therapy with immunostimulatory effect which should be discontinued for 4 weeks or more than 5 half-lives; and antibody drugs which should be discontinued for ≥ 12 weeks (≥ 4 weeks after discontinuation of bevacizumab or nimotuzumab is acceptable); moreover, all treatment-emergent adverse events (TEAEs, except for alopecia) should have stabilized and recovered to the level specified in the eligibility criteria or ≤ Grade 1 toxicity (NCI CTCAE V.5.0); 10) Subjects of childbearing potential (male or female) must use effective medical contraception during the study and for 6 months after the end of dosing. Women of childbearing potential must have a negative pregnancy test within 72 h before the first dose; 11) Subjects voluntarily participate in the study, sign the ICF, and will be able to comply with the protocol-specified visits and relevant procedures.
Exclusion Criteria	Subjects who meet any of the following criteria will be excluded: 1) Subjects with locally advanced disease will not be screened if they can receive radical treatment such as surgery, radical radiotherapy, or radical chemoradiotherapy; 2) Metastases to central nervous system; 3) History of other malignancies (except for non-melanoma skin cancer in situ, superficial bladder cancer, cervical cancer in situ, gastrointestinal intramucosal cancer, breast cancer, localized prostate cancer that have been cured and have not recurred within 5 years, which are considered acceptable for enrollment by the investigator); 4) History of severe allergic diseases, history of serious drug allergy, and known allergy to macromolecular protein preparations or any component of the KL-A167 Injection formulation; 5) Prior treatment with anti-PD-1 antibody, anti-PD-L1 antibody, anti-PD-L2 antibody, anti-CTLA-4 antibody, or CAR-T cells (or any other antibody acting on T-cell co-stimulation or checkpoint pathway); 6) Palliative radiotherapy (except for bone metastases) scheduled for symptom control during the study; 7) Other systemic anti-tumor therapies that may be received during the study; 8) Prior anti-tumor vaccine within 3 months prior to the first dose; 9) Allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation or autologous hematopoietic stem cell transplantation within 3 months prior to the first dose; 10) Active infection, or unexplained fever before the first dose; 11) Systemic use of antibiotics within 1 week prior to signing the ICF; 12) Any active autoimmune disease or history of autoimmune disease, including, but not limited to, immune-related neurological disorders, multiple sclerosis, autoimmune

	(demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis, systemic lupus erythematosus (SLE), connective tissue disorder, scleroderma, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, autoimmune hepatitis, toxic epidermal necrolysis (TEN), or Stevens-Johnson syndrome; 13) Subjects with hyperthyroidism and organic thyroid disease will not be screened, but those with hypothyroidism treated with a stable dose of thyroid hormone replacement therapy can be enrolled; 14) Systemic treatment with steroids (at a dose equivalent to prednisone > 10 mg/day) or other immunosuppressants within 14 days prior to the first dose; Note: Adrenaline replacement therapy at doses equivalent to prednisone ≤ 10 mg/day is allowed for subjects without active immune disease. Topical, intraocular, intra-articular, intranasal, or inhaled corticosteroids (with minimal systemic absorption) are permitted; and short-term use of corticosteroids for prophylaxis (e.g., contrast allergy) or treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity caused by contact allergens) is permitted. 15) Subjects with serious medical conditions, such as cardiovascular disorders like Grade III or higher abnormal cardiac function (NYHA criteria), ischemic heart disease (such as myocardial infarction or angina pectoris), poorly controlled diabetes mellitus (fasting serum glucose ≥ 10 mmol/L), poorly controlled hypertension (systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg), and ejection fraction < 50% by echocardiography; 16) QTc interval > 450 msec for males and > 470 msec for females; 17) Abnormal ECG findings and additional risks associated with the use of the investigational product in the opinion of the investigator; 18) Presence of active hepatitis B (HBV DNA ≥ 2000 IU/mL or 10^4 copies/mL) or hepatitis C (positive for hepatitis C antibody and HCV RNA above the lower limit of detection of the assay); 19) Known history of human immunodeficiency virus (HIV)-positive or known history of acquired immunodeficiency syndrome (AIDS); 20) Subjects with known history of interstitial pneumonia, noninfectious pneumonitis, or highly suspicious of interstitial pneumonia; or subjects with conditions that may interfere with the detection or management of suspected drug-related pulmonary toxicity; and asymptomatic subjects with prior drug-induced or radiation noninfectious pneumonitis are allowed to be enrolled; 21) Active pulmonary tuberculosis, or previous history of tuberculosis infection but not controlled by treatment; 22) Subjects who have received immunotherapy and experienced ≥ Grade 3 immune-related adverse reactions (ADRs);

	23) Use of any active vaccine against infectious diseases (e.g. influenza vaccine, varicella vaccine, etc.) within 4 weeks prior to the first dose or planned to be used during the study; 24) Previous confirmed history of neurological or mental disorders, including epilepsy or dementia; 25) History of definite drug abuse or alcohol abuse within 3 months; 26) Pregnant or lactating women; 27) Participation in other clinical trials within 1 month prior to the first dose; 28) Other factors that may affect the efficacy or safety evaluation of this study in the opinion of the investigator.
Physical Examination of Subjects	The subject undergoes a full physical examination at screening, including demographic data, medical history, height, weight, histopathological diagnosis, CT/MRI, biomarkers, testing of Epstein-Barr virus DNA copies, vital signs, physical examination, ECOG score, ECG, echocardiography, laboratory tests (hematology, blood chemistry, urinalysis, coagulation, thyroid function, lymphocyte subsets, virological examination, blood pregnancy [for women of childbearing potential only]), AEs, and concomitant medications. Re-examination may be performed and recorded at screening if deemed necessary by the investigator. A physical examination and recording of AEs should be performed at each visit as required.
Efficacy Evaluation	Primary efficacy measure: ORR assessed by the Independent Review Committee using RECIST v1.1. It refers to the fact that objective anti-tumor efficacy is assessed per RECIST v1.1, and BOR would be calculated by taking the number of subjects with CR/PR and dividing it by the total number of subjects. Secondary efficacy measure: ORR, PFS, DoR, TTR assessed by the investigator per RECIST v1.1 and irRECIST, and OS.
Safety Evaluations	Safety evaluations will be performed at screening, during the treatment period, and through the Safety Follow-up Visit. Subjects who withdraw prematurely must receive safety evaluation prior to the withdrawal. Safety observation variables include: AEs, laboratory tests, vital signs, physical examination, ECOG score, ECG, echocardiography, and early withdrawal due to safety or tolerability reasons, etc.
Immunogenicity Evaluation	**Immunogenicity Blood Sampling Time Points** Blood sampling for testing will be performed within 24 h before dosing on Day 1 of each cycle, at the withdrawal visit and follow-up visit (in case of hospital visit). **Blood Sampling and Blood Sample Processing** Immunogenicity blood sampling and blood sample processing are detailed in the Central Laboratory Operations Manual. **Immunogenicity Test** Anti-drug antibodies (ADAs) in the blood samples of subjects will be tested before and after

	dosing, and the neutralizing antibodies (NAbs) analysis will be determined based on the results of the study.
Biomarker Evaluation	Subjects will be required to have blood drawn at screening. Archival tumor tissues should be provided, otherwise, fresh tumor tissues will be collected for biomarker testing at screening. **Blood Sampling and Blood Sample Processing** Biomarker blood sampling and blood sample processing are detailed in the Central Laboratory Operations Manual. **Provision or Collection of Tumor Tissues** Subjects should provide archival tumor tissues or have fresh tumor tissues taken for biomarker analysis at screening. Newly obtained tissues are preferred, and archival and preserved tumor tissues may be provided for patients who do not have newly obtained tissues. The requirements for the provision or collection of tumor tissues are detailed in the Central Laboratory Operations Manual. **Biomarker Testing** The expression of sPD-L1 in blood samples of subjects, and the expression of PD-L1 in tumor tissues will be detected.
PK Evaluation	**PK Blood Sampling Points** There will be a total of 2 blood sampling time points in each cycle for Cycles 1-5: within 1 h before dosing and within 30 min after the end of dosing on Day 1. **Blood Sampling and Blood Sample Processing** PK blood sampling and blood sample processing are detailed in the Central Laboratory Operations Manual. **Plasma Concentration Test** The drug concentration of KL-A167 in blood samples will be measured. **Main Parameters of PK Analysis** C_{max} and C_{min} will be statistically described according to the scheduled blood sampling points. Population PK analyses may be performed, as appropriate, in combination with plasma concentration data obtained from other clinical trials of KL-A167. PK parameters include C_{max}, C_{min}, T_{max}, $AUC_{0-\infty}$, AUC_{0-t}, $T_{1/2}$, V_{ss}, CL estimated by the population PK model.
Data Processing and Statistical Analysis	**Data Management** An electronic data capture (EDC) system is used for data management in this study. **Efficacy Analysis** The 95% CI of ORR will be estimated using the Clopper-Pearson method, and the drug can be considered effective when the lower limit of the CI of the subject is not less than 15%. The Kaplan-Meier method will be used to estimate the median and 95% CIs of PFS, OS, DOR, TTR and corresponding survival curves will be plotted.

	Safety Analysis Based on the safety analysis set (SAS), safety variables will be assessed using the SAS. Safety variables include AEs, physical examinations, vital signs, ECOG score, laboratory tests, ECGs, echocardiography, and early withdrawal due to safety or tolerability reasons, etc. The entire test items of physical examinations, laboratory tests, ECGs, and echocardiograms will be listed in a pre- and post-treatment cross-tabulation (based on normal ranges and clinical significance as judged by the investigator). Changes in vital signs and ECOG scores over time will be listed. Abnormal tests after treatment will be presented in lists. All AEs occurring during this clinical study will be coded using MedDRA, and the number of subjects and number of events for AEs will be listed in detail by SOC/PT classification. **Immunogenicity Analysis** Immunogenicity assessment data will be presented according to the categories listed below. These data include number and percentage of subjects with positive ADA test results at baseline, number and percentage of subjects with at least one positive ADA test result at any time point after the first dose, number and percentage of subjects with treatment-induced positive ADA test results at any time point after the first dose, and number and percentage of subjects with treatment-enhanced positive ADA test results at any time point after the first dose. **PK Analysis** The plasma concentration data of KL-A167 obtained in this study will be subjected to descriptive statistical analysis. Population PK analyses may be performed, as appropriate, in combination with plasma concentration data obtained from other clinical trials of KL-A167. PK parameters mainly include C_{max}, C_{min}, T_{max}, $AUC_{0-\infty}$, AUC_{0-t}, $t_{1/2}$, V_{ss}, CL estimated by the population PK model. **Exploratory Analysis** The expression levels and distribution of PD-L1 and sPD-L1 will be analyzed descriptively, and their potential relationship with efficacy will be explored. The analysis will be performed based on data collection.
Study Duration	This study is expected to end 12 months after the first dose of the last subject. At the end of the study, subjects who voluntarily receive continued treatment and who, in the opinion of the investigator, may continue to benefit from continued treatment can sign the ICF for continued treatment until confirmed PD, or voluntary withdrawal of informed consent by the subject, or no more benefits for the subject as considered by the investigator, or death or marketing approval of the KL-A167 Injection for this indication, whichever occurs first. Notes: Benefit to the subject refers to the situation where the subject has not progressed according to the tumor assessment criteria, the disease of subject remains under control (disease response or stable disease), and the subject voluntarily agrees to continue the

	treatment; or the situation where the subject experiences PD as specified in the tumor assessment criteria, but the investigator determines that the possible benefit of the continued treatment outweighs the risk, and the subject voluntarily agrees to continue the treatment.

Study Schedule

Item		Screening/Baseline	Treatment Period		Withdrawal Visit[q]	Safety Follow-up[r]	Survival Follow-up[s]
			C1	C_N*			
Time		-D14 ~ -D1	D1	D1±2	Within 7 days after confirmed withdrawal	Day 30 ±5 days after completion of the withdrawal visit	After safety follow-up visit Every 30 ±7 days
ICF		X					
Demographic data, medical history[a]		X					
Height, weight[b]		X		X	X		
Histopathological diagnosis		X					
★ CT/MRI[c]		X	See notes		X		
Biomarker[d]		X					
Epstein-Barr virus DNA copy number test[e]		X	See notes				
Vital signs[f]		X	X	X	X		
Physical examination		X		X	X		
ECOG score		X		X	X		
Laboratory tests	Hematology/blood chemistry/urinalysis/coagulation[g]	X		X	X		
	Thyroid function (TSH, FT4, FT3)[h]	X		X	X		
	Lymphocyte subsets[i]	X	See notes				
	Virological examination[j]	X					
	Pregnancy test[k]	X					
ECG		X		X	X		
★ Echocardiography		X			X		
Inclusion/exclusion criteria		X					
Administration			X	X			
Dose eligibility assessment[l]				X			
Immunogenicity[m]			See notes				
PK[n]			See notes				
AEs[o]		X					

Concomitant medications[p]	X	

Notes:

* Relevant tests specified in the protocol should be performed before dosing in subsequent cycles, and the test results within 2 days before dosing are acceptable. In the event of a dose delay, the scheduled visit items at the same time point should be delayed accordingly to ensure consistency with the actual dosing time.

★ The test results of CT/MRI and echocardiography obtained in this hospital at screening are acceptable within 28 days before dosing.

a) Demographic data include date of birth, gender, ethnicity, racial, age, etc. Medical history includes current medical history (especially diagnostic information of tumor), prior medical history, medication history, immunization history, allergy history, smoking history, alcohol consumption history, areca nut consumption history, drug abuse history, blood transfusion history, clinical trial history, surgical history, and radiotherapy history, etc.

b) Height will be measured at screening only, and weight will be measured at screening, before dosing in each cycle, and at the withdrawal visit.

c) CT/MRI examination: It mainly refers to the examination of nasopharynx, head, neck, chest, abdomen and pelvis. If there is no contraindication, enhanced scan is preferred. The same imaging method should be used during the study for the same lesion. Bone scan at screening will be performed at the discretion of the investigator. During the treatment period, efficacy will be evaluated every 6 weeks on the last day from the first dose, with a time window of no more than ±5 days. Subjects with persistent disease response may undergo imaging assessments every 12 weeks (±5 days) if 24 months has elapsed after the first dose. Each response assessment should be performed as planned, even in the event of a dose delay.

- Imaging examination may be performed at least 4 weeks apart in case of PD and if deemed necessary by the investigator.
- Imaging examination should be performed in a timely manner at the withdrawal visit (no re-examination is required if no more than 4 weeks has elapsed after the last imaging examination).
- In addition to radiologically confirmed PD, subjects who discontinue treatment for other reasons should also undergo imaging examination every 6 weeks (±5 days) after withdrawal until documented PD or start of new anti-tumor therapy or lost to follow-up or death.

d) Biomarkers: Subjects will be required to have blood drawn at screening. Archival tumor tissues should be provided, otherwise, fresh tumor tissues will be collected for biomarker testing at screening. This test is performed by a third-party testing unit in accordance with their central laboratory SOPs.

e) Epstein-Barr virus DNA copy number test: Blood samples for this test should be collected at screening, each efficacy assessment, and the withdrawal visit. This test is performed by a third-party testing unit in accordance with their central laboratory SOPs.

f) If the vital signs at screening are observed more than 2 days from the first dose, they should be repeated within 2 days before dosing. Vital signs should be observed within 2 days before dosing, within 1 h after the end of dosing, and at the withdrawal visit in each cycle.

g) If hematology, blood chemistry, urinalysis and coagulation tests at screening are performed more than 7 days from the first dose, they should be repeated 7 days to 1 day

before dosing, and pre-dose on Day 1 of each subsequent cycle, and at the withdrawal visit.

h) Thyroid function: TSH, FT4 and FT3 will be tested within 14 days prior to the first dose, and pre-dose on Day 1 of each subsequent cycle and at the withdrawal visit.

i) Lymphocyte subsets: it will be performed at screening, at each efficacy assessment, and at the withdrawal visit.

j) Virological examination includes hepatitis B (five items), hepatitis C virus antibody (HCV-Ab), treponema pallidum antibody (TP-Ab), and human immunodeficiency virus antibody (HIV (1 + 2) Ab). Hepatitis B virus DNA (HBV-DNA) should be tested if hepatitis B surface antigen (HBsAg) is positive, and hepatitis C virus RNA (HCV-RNA) should be tested if HCV antibody is positive.

k) A blood pregnancy test (chorionic gonadotropin) will be performed at screening for women of childbearing potential only and blood pregnancy test results within 72 h before dosing are acceptable.

l) Dose eligibility assessment: AEs in the previous cycle do not meet the criteria for treatment interruption and/or discontinuation.

m) Immunogenicity: Blood sampling will be performed within 24 h before dosing on Day 1 of each cycle, at the withdrawal visit and follow-up visit (in case of hospital visit).

n) PK: There will be a total of 2 blood sampling time points in each cycle for Cycles 1-5: within 1 h before dosing and within 30 min after the end of dosing on Day 1.

o) AEs: AEs should be observed and recorded from the time of signing the ICF at screening until the end of the safety follow-up visit (if the subject starts a new anti-tumor therapy after withdrawal from the group, newly occurred AEs after that point will not be recorded). The existing AEs should be followed until the event disappears, resolves, or recovers to the level specified in the eligibility criteria, or is stable and no further follow-up is required as considered by the investigator, or initiation of a new anti-tumor therapy, or until lost to follow-up, or death, or the event can be otherwise explained.

p) Concomitant medications should be recorded from the time of signing the ICF at screening to the end of the safety follow-up visit (if the subject starts a new anti-tumor therapy after withdrawal from the group, concomitant medications will no longer be recorded).

q) Withdrawal visit should be performed within 7 days after the determination of withdrawal for any reason, and the specific time of withdrawal examination should be determined by the investigator according to the actual situation. If CT/MRI is completed within the first 4 weeks of the withdrawal visit, and laboratory tests, ECGs, echocardiography, immunogenicity blood sampling, and blood sampling for Epstein-Barr virus DNA copy number are completed within the first 7 days, then these tests will not be required at this stage.

r) Follow-up visit will be performed on Day 30 ± 5 days after the completion of the withdrawal visit in the form of a hospital visit or telephone follow-up visit based on the specific condition of the subject. Immunogenicity blood sampling will be performed at hospital follow-up visits; otherwise, safety will be followed up via telephone calls.

s) Survival follow-up: Survival follow-up is required for all patients. It will be performed once every 30 ± 7 days after the safety follow-up visit by telephone or hospital visit to record the survival of the patient until death or lost to follow-up of the subject. If the patient is lost to follow-up, the survival cutoff date is the date when the patient is last known to be alive.

Table of Contents

1 Introduction

1.1 Study Rationale

Tumor is a malignant disease that poses a severe threat to public health. The incidence of malignant tumors in China accounts for 25.49% of that of the world, ranking the first worldwide. Among the top 10 malignant tumors in terms of incidence in China, except for cervical cancer, which ranks the second in the world, the other 9 malignancies rank the first in terms of incidence in the world. Lung cancer, liver cancer, gastric cancer, thyroid cancer, brain, and central nervous system tumors account for more than 34.00% of the incidence in the world, and esophageal cancer accounts for 62.90% of the incidence in the world. Although the incidence of NPC is low in most parts of the world, it is still high in southern China, Mediterranean and other regions [1]. In 2012, 86,500 new cases of NPC were reported worldwide, 71% of which occurred in eastern and southeastern Asia, and the prognosis of NPC remains poor at present [2]. The annual direct cost of cancer treatment in China is nearly 100 billion yuan, which poses a huge economic burden on patients and even the whole society. Therefore, tumor not only poses a serious threat to human health, causes great pain to patients and heavy economic burden to families, but also huge consumption of social medical resources.

Anti-PD-1 (Programmed death-1)/PD-L1 (Programmed death ligand-1) monoclonal antibody can block the binding of PD-1 to PD-L1, relieve the inhibition of immune function exerted by tumor cells, and activate immune function, thereby killing tumor cells. A variety of inhibitors targeting this pathway have been developed, and multiple PD-1/PD-L1 antibodies have been marketed worldwide, including nivolumab, pembrolizumab, toripalimab, sintilimab, camrelizumab, tislelizumab, durvalumab, and atezolizumab. The results of several clinical studies have also confirmed that PD-1/PD-L1 inhibitors have secured remarkable achievements in malignant tumors at present. Released clinical data showed that anti-PD-1/PD-L1 monoclonal antibodies have significant advantages over previous treatments in terms of efficacy and safety.

This product is a recombinant humanized monoclonal anti-PD-L1 produced by the expression system in the Chinese hamster ovary (CHO) cells based on the recombinant DNA technology, and has been evaluated for preclinical PD, PK and toxicology in order to show good clinical efficacy and safety in the treatment of NPC.

1.2 Study Background

1.2.1 Mechanism of Action

PD-L1/PD-1 signaling pathway is an important pathway involved in the immune escape mechanism of tumors. PD-L1 (also known as B7-H1) is categorized as a type I transmembrane protein as the main ligand of PD-1. It is widely expressed on the surface of a variety of cells, including T cells, B cells, monocytes, macrophages, and dendritic cells; meanwhile, it is also expressed in tissues such as

placenta, eyes and their epithelium, skeletal muscle, and other tissues [3]. PD-1 (also known as CD279) is an immunosuppressive receptor that is widely expressed on the surface of activated T cells, B cells, monocytes and dendritic cells. The binding of PD-L1 to PD-1 promotes the phosphorylation of tyrosine in the domain of immunoreceptor tyrosine-based switch motif (ITSM) in the cytoplasmic region of PD-1, recruits SHP-2 phosphatase (Src homology 2 domain-containing protein tyrosine phosphatase 2), which leads to dephosphorylation of ZAP70 (Zeta-chain-associated protein kinase 70), a key molecule in the downstream T cell antigen receptor (TCR) signaling pathway, AKT (also known as PKB, protein kinase B), PI3K (phosphatidyl inositol-3-kinase) and PKC (protein kinase C), and ultimately inhibits the transcription and translation of genes and cytokines required for T cell activation, thereby negatively regulating T-cell activity (Figure 1) [4-6].

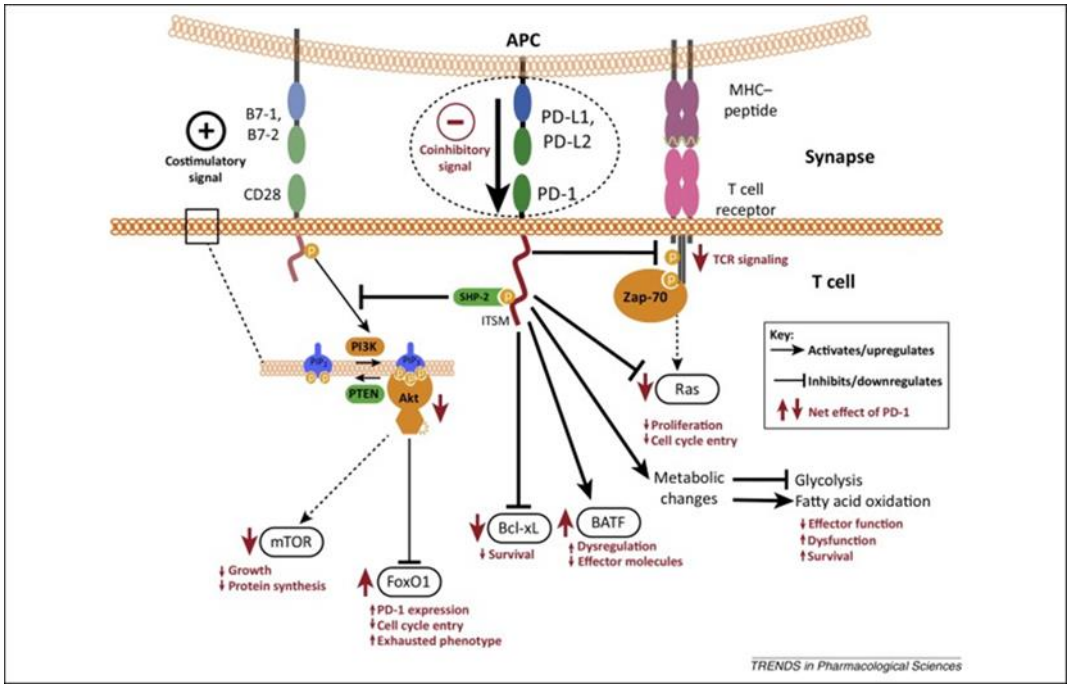

Figure 1 PD-L1/PD-1 Signaling Pathway [6]

Normally, the PD-L1/PD-1 signaling pathway can induce and maintain immune tolerance of peripheral tissues through the above-mentioned mechanisms, and plays a positive role in preventing hyper-inflammatory reaction of tissues and development of auto-immune diseases. However, in a variety of solid tumors such as lung cancer, melanoma, breast cancer, glioma, lymphoma, digestive tract tumor and reproductive system tumors, PD-L1 is over-expressed on the surface of tumor cells [7], and after binding to PD-1, it leads to tumor immune escape and promote tumor growth through its inhibitory effect on lymphocytes. Anti-PD-L1 and anti-PD-1 antibodies can relieve the inhibition of T cells exerted by the PD-L1/PD-1 signaling pathway through blocking the binding of PD-L1 on the surface of tumor cells to PD-1 on T cells, thereby exerting the anti-tumor therapeutic effects. At present, PD-L1/PD-1 blockers have shown favorable clinical therapeutic efficacy in a variety of solid tumors, especially melanoma and non-small cell lung cancer, and drugs targeting this signaling

pathway have been marketed successively.

The KL-A167 Injection (R&D code: A167) is a humanized IgG1κ isoform monoclonal antibody molecule directed against the PD-L1/PD-1 signaling pathway, with independent intellectual property rights. It can specifically target PD-L1 and block the PD-L1/PD-1 signaling pathway, relieve the inhibition on T cells, thereby exerting therapeutic effects. The mechanism of action of KL-A167 Injection has been fully validated in the nonclinical PD studies: KL-A167 Injection could specifically target human PD-L1, block the binding of PD-L1 to PD-1, so as to inhibit the activation of PD-L1/PD-1 signaling pathway, inhibit tumor immune escape, enhance the immune response of the body, thereby inhibiting tumor growth and exerting anti-tumor effect.

1.2.2 Nonclinical Studies

In terms of PD, KL-A167 Injection can specifically bind to the PD-L1 of human and cynomolgus monkey *in vitro*, with species selectivity higher than that of the control drug Tecentriq; it can relieve the inhibition of DCs on T cell secretion of cytokines and T cell proliferation, and significantly inhibit the activity of Treg cells at the same time; and it has no obvious ADCC (antibody-dependent cell-mediated cytotoxicity) effect, which further increases safety. *In vivo*, KL-A167 Injection specifically inhibits the subcutaneous growth of xenografts that express human PD-L1 in mice, prolong the survival time and improve the survival rate of mice transplanted with intraperitoneal tumor cells. Overall, *in vitro* and *in vivo* PD studies have demonstrated clear mechanism of action of KL-A167 Injection, the PD of which is comparable to the that of the control drug Tecentriq.

In terms of PK, after a single intravenous injection of KL-A167 Injection to cynomolgus monkeys, it is mainly distributed in blood with slow elimination. The serum drug concentration and exposure of KL-A167 Injection (1-20 mg/kg) in cynomolgus monkeys increased with the increase of the administered dose, demonstrating non-linear PK profiles, without gender difference in the main PK parameters of each dose group. After multiple doses, ADAs were detected in most cynomolgus monkeys (7/8), which was presumed to be the main reason for big differences in individual PK parameters after the last dose. Tissue distribution study in KL-A167 tumor-bearing mice showed that the total radioactivity was mainly distributed in plasma after a single intravenous dose of KL-A167 to tumor-bearing mice, and the radioactivity concentrations distributed in tumors and tissues were lower than those in plasma at the same time points. The total radioactivity in the tumor increased continuously after administration, with the highest total radioactivity distributed in the tumor at the last collection (accounting for 9.21% of the total administered dose), while the radioactivity of liver, one of the non-target tissues with the highest total radioactivity, accounted for only about 0.77% of the administered dose (approximately 11.83% of the C_{max} in liver), demonstrating that KL-A167 Injection could specifically recognize and aggregate in tumor tissues with high PD-L1 expression,

while with less distribution and faster clearance in non-target tissues. Overall, KL-A167 Injection can specifically recognize and aggregate in tumor tissues with high PD-L1 expression, and has good *in vivo* PK behavior.

In terms of safety, the general pharmacology results showed that the KL-A167 Injection had no effect on cardiovascular and respiratory systems of cynomolgus monkeys, nor on the nervous and respiratory systems in rats. The results of the single-dose toxicity study showed that the maximum tolerated dose (MTD) was 600 mg/kg in cynomolgus monkeys. In the 4-week repeat-dose toxicity study in cynomolgus monkeys, 0/10, 1/10 and 3/10 animals in the 20, 60, and 200 mg/kg dose groups showed slight mononuclear cell infiltration in the cerebral/cerebellar choroid plexus, respectively, which was mild in severity and recovered after an 8-week recovery period. The no observed adverse effect level (NOAEL) in this study was 60 mg/kg. Based on the results of the preclinical PK study, it is presumed that the clinical efficacy of KL-A167 is comparable to the marketed drug Atezolizumab (Tecentriq®), the clinical human dose of which is 20 mg/kg), and these two drugs have the same target. The dose levels of 20, 60, and 200 mg/kg are equivalent to 1, 3 and 10-fold the proposed clinical dose of 20 mg/kg KL-A167 Injection. ADAs to KL-A167 Injection were detected across the dose groups of 20-200 mg/kg, with a neutralizing effect, demonstrating immunogenicity of this drug. Combined with the results of toxicokinetic studies, the exposure in each dose group was positively correlated with dose, and the appearance of NAbs had no significant effect on the *in vivo* exposure of the drug. No effects of the KL-A167 Injection on the menstrual cycle and reproductive system of cynomolgus monkeys were observed in the reproductive toxicity study in cynomolgus monkeys (with concomitant long-term toxicity study). However, based on the characteristics of target tissue distribution (PD-L1 was expressed in tissues such as human placenta), it is recommended that comprehensive consideration should be given to the clinical safety of drug use in special populations. The cross-reactivity results showed that the types of cross-reactivity of KL-A167 Injection to human and cynomolgus monkey tissues were basically the same. The organs with cross-reaction with KL-A167 Injection were lungs, spleen, lymph nodes, placenta and thymus. No toxic manifestations were observed in the above tissues in preclinical toxicology studies, demonstrating limited significance of tissue cross-reactivity results as a reference. However, it is recommended that attention should be paid to the adverse reactions of organs with cross-reactions, such as lungs, spleen, lymph nodes, placenta and thymus, during the clinical period. KL-A167 Injection did not cause hemolysis and local irritation. Overall, KL-A167 Injection showed few toxicities and side effects, and demonstrated good safety in multiple pivotal toxicity studies.

1.2.3 Clinical Studies

Based on the available data from the currently ongoing clinical studies of KL-A167 Injection (KL167-

Ia-01, KL167-I-02, KL167-Ib-04, etc.), KL-A167 Injection has shown preliminary efficacy in a variety of lymphomas and solid tumors, such as Hodgkin's lymphoma, NK/T lymphoma, NPC, squamous cell carcinoma of head and neck, etc. See the Investigator's Brochure (IB) for details (V4.0, 01 Dec, 2020).

1.2.4 Development of Similar Drugs

The PD-1/PD-L1 signaling pathway is an important signaling pathway in tumor escape. Anti-PD-1/PD-L1 therapy has become a hot target for solid tumors in recent years. Blockade of PD-1/PD-L1 signaling can promote the proliferation of tumor antigen-specific T cells and kill tumor cells.

Several PD-1/PD-L1 monoclonal antibodies have been marketed worldwide, including nivolumab, pembrolizumab, toripalimab, sintilimab, camrelizumab, tislelizumab, durvalumab, and atezolizumab, etc. Meanwhile, multiple PD-1/PD-L1 monoclonal antibodies are being investigated in clinical phase 1 or 2 studies, and have been extensively studied in multiple indications.

1.3 Risk/Benefit Evaluation

1.3.1 Identified Potential Risks

Based on its clinical data, the marketed anti-PD-L1 monoclonal antibodies were well tolerated. Only a small proportion of subjects discontinued the drug due to ADRs, and most of the ADRs were manageable or resolved after treatment.

1.3.2 Identified Potential Benefits

The marketed anti-PD-1/PD-L1 monoclonal antibodies have secured remarkable achievements in several clinical studies of malignant tumors. However, KL-A167 Injection has shown preliminary efficacy in patients with solid tumors and lymphoma.

1.3.3 Evaluation of Potential Risks and Benefits

Immune-related ADRs are the common reactions of anti-PD-1/PD-L1 monoclonal antibody with variable symptoms. The investigator should pay special attention to the early symptoms and signs of immune-related reactions in clinical studies, make timely and correct judgment, adjust the medication according to the protocol and give appropriate treatment to reduce the risk of drug use by the subjects.

The mechanism of action of this product is clear. Based on the nonclinical study results and the current clinical study data of this product, as well as clinical experience with similar products, this product may potentially benefit patients with NPC.

In summary, appropriate variables will be adopted in this study to reduce the potential risks and minimize the risks to subjects. Moreover, based on the nonclinical study results and the current clinical study data of this product, as well as clinical application experience of similar products, it is expected that this product may bring potential benefits to patients with NPC.

2 Study Objectives

2.1 Primary

To evaluate the ORR of KL-A167 Injection in patients with recurrent or metastatic NPC, as assessed by the Independent Review Committee using Response Evaluation Criteria in Solid Tumors v1.1 (RECIST 1.1).

2.2 Secondary

1) To evaluate the investigator-assessed ORR of KL-A167 Injection in patients with recurrent or metastatic NPC as per RECIST V1.1 and irRECIST, respectively;
2) To evaluate PFS, OS, DCR, DoR, and TTR of KL-A167 Injection in patients with recurrent or metastatic NPC;
3) To evaluate the PK characteristics of KL-A167 Injection in patients with recurrent or metastatic NPC;
4) To evaluate the safety of KL-A167 Injection in patients with recurrent or metastatic NPC;
5) To evaluate the immunogenicity of KL-A167 Injection in patients with recurrent or metastatic NPC.

2.3 Exploratory

To evaluate the correlation between the expression of biomarkers (PD-L1 and sPD-L1) and treatment response.

3. Study Design

3.1 Overall Design

This is a single-arm, open-label, multicenter study to evaluate the efficacy and safety of KL-A167 Injection in patients with recurrent or metastatic NPC who have failed ≥ 2 lines of chemotherapy. A schematic of the overall study design is presented in Figure 2.

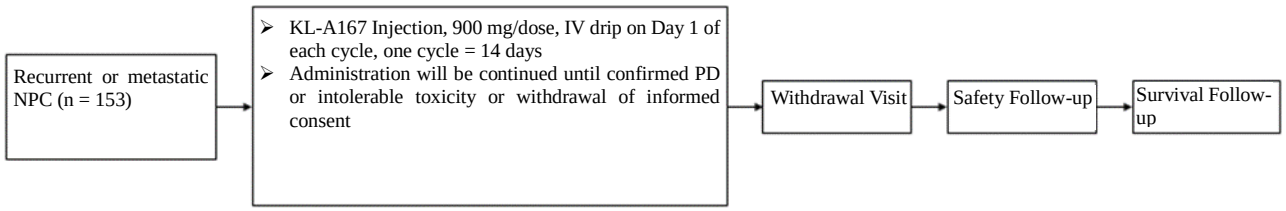

Figure 2 Schematic Diagram of the Overall Study Design

3.2 Rationale for Dose Selection

Clinical study data of KL-A167 Injection Phase I clinical studies in the treatment of lymphomas and solid tumors showed that the drug basically exhibited a linear PK profile over the dose range of 600 to 1500 mg/human, with a half-life ranging from 12 to 14.8 days, which conformed to the dosing design with a two-week interval. Although PR was observed with KL-A167 Injection over the dose range of 600 to 1200 mg Q3W in Phase I clinical studies in the treatment of lymphomas and solid

tumors, the dose of KL-A167 Injection at 900 mg Q2W achieved exposures (AUC) similar to that of 1200 mg Q3W, and maintained a more stable concentration-time curve (low $C_{max,ss}$, high $C_{min,ss}$). Theoretically, high $C_{min,ss}$ can help maintain high receptor occupancy (RO). Moreover, KL-A167 Injection 900 mg Q2W has shown potential efficacy in Phase 2 studies in the treatment of lymphoma. Therefore, the dosing regimen of 900 mg Q2W was selected for KL-A167 Injectionin in this study.

3.3 Study End Time

This study is expected to end 12 months after the first dose of the last subject. At the end of the study, subjects who voluntarily receive continued treatment and who, in the opinion of the investigator, may continue to benefit from continued treatment can sign the ICF for continued treatment until confirmed PD, or voluntary withdrawal of informed consent by the subject, or no more benefits for the subject as considered by the investigator, or death or marketing approval of the KL-A167 Injection for this indication, whichever occurs first.

Notes: Benefit to the subject refers to the situation where the subject has not progressed according to the tumor assessment criteria, the disease of subject remains under control (disease response or stable disease), and the subject voluntarily agrees to continue the treatment; or the situation where the subject experiences PD as specified in the tumor assessment criteria, but the investigator determines that the possible benefit of the continued treatment outweighs the risk, and the subject voluntarily agrees to continue the treatment.

4 Study Population

4.1 Inclusion Criteria

Subjects may be entered in the study only if they meet all of the following criteria:

1) Aged ≥ 18 years old, male or female;
2) Subjects with histopathologically confirmed recurrent/metastatic nonkeratinizing differentiated or undifferentiated NPC;
3) Subjects with diseases of clinical stage IVB [AJCC (8th edition)] who have received first line of platinum-containing combination chemotherapy and second line of monotherapy or failure of combination therapy;
4) Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1;
5) Expected survival ≥ 12 weeks;
6) Subjects with at least one measurable lesion according to RECIST v1.1, and lesions that have been treated with local therapies, such as radiotherapy, cannot be considered as measurable lesions;
7) Tissue or tissue samples must be provided for biomarker analysis. Newly obtained tissues are preferred, and archived paraffin slices may be provided for patients who do not have

newly obtained tissues;

8) Adequate organ and bone marrow function, as defined below:
   a) Hematology: neutrophil count (NEUT #) ≥ 1.5 × 10^9/L; platelet count (PLT) ≥ 90 × 10^9/L; hemoglobin concentration ≥ 9 g/dL;
   b) Hepatic function: AST and ALT ≤ 3 × ULN; TBIL ≤ 1.5 × ULN; ALT and AST ≤ 5 × ULN for subjects with liver metastases; TBIL ≤ 2 × ULN for subjects with liver metastases or Gilbert's syndrome;
   c) Renal function: creatinine clearance (CCR) ≥ 50 mL/min;
   d) Coagulation function: INR ≤ 1.5 and APTT ≤ 1.5 × ULN;
9) Subjects who have taken chemotherapeutic drugs which should be discontinued for ≥ 4 weeks before the first dose (mitomycin or nitrosoureas should be discontinued for ≥ 6 weeks); received surgery, molecular targeted therapy, traditional Chinese medicine therapy with anti-tumor indications, radiotherapy, and anti-tumor therapy with immunostimulatory effect which should be discontinued for 4 weeks or more than 5 half-lives; and antibody drugs which should be discontinued for ≥ 12 weeks (≥ 4 weeks after discontinuation of bevacizumab or nimotuzumab is acceptable); moreover, all TEAEs (except for alopecia) should have stabilized and recovered to the level specified in the eligibility criteria or ≤ Grade 1 toxicity (NCI CTCAE V.5.0);
10) Subjects of childbearing potential (male or female) must use effective medical contraception during the study and for 6 months after the end of dosing. Women of childbearing potential must have a negative pregnancy test within 72 h before the first dose;
11) Subjects voluntarily participate in the study, sign the ICF, and will be able to comply with the protocol-specified visits and relevant procedures.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded:

1) Subjects with locally advanced disease will not be screened if they can receive radical treatment such as surgery, radical radiotherapy, or radical chemoradiotherapy;
2) Metastases to central nervous system;
3) History of other malignancies (except for non-melanoma skin cancer in situ, superficial bladder cancer, cervical cancer in situ, gastrointestinal intramucosal cancer, breast cancer, localized prostate cancer that have been cured and have not recurred within 5 years, which are considered acceptable for enrollment by the investigator);
4) History of severe allergic diseases, history of serious drug allergy, and known allergy to macromolecular protein preparations or any component of the KL-A167 Injection

formulation;

5) Prior treatment with anti-PD-1 antibody, anti-PD-L1 antibody, anti-PD-L2 antibody, anti-CTLA-4 antibody, or CAR-T cells (or any other antibody acting on T-cell co-stimulation or checkpoint pathway);
6) Palliative radiotherapy (except for bone metastases) scheduled for symptom control during the study;
7) Other systemic anti-tumor therapies that may be received during the study;
8) Prior anti-tumor vaccine within 3 months prior to the first dose;
9) Allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation or autologous hematopoietic stem cell transplantation within 3 months prior to the first dose;
10) Active infection, or unexplained fever before the first dose;
11) Systemic use of antibiotics within 1 week prior to signing the ICF;
12) Any active autoimmune disease or history of autoimmune disease, including, but not limited to, immune-related neurological disorders, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis, systemic lupus erythematosus (SLE), connective tissue disorder, scleroderma, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, autoimmune hepatitis, toxic epidermal necrolysis (TEN), or Stevens-Johnson syndrome;
13) Subjects with hyperthyroidism and organic thyroid disease will not be screened, but those with hypothyroidism treated with a stable dose of thyroid hormone replacement therapy can be enrolled;
14) Systemic treatment with steroids (at a dose equivalent to prednisone > 10 mg/day) or other immunosuppressants within 14 days prior to the first dose;

    Note: Adrenaline replacement therapy at doses equivalent to prednisone ≤ 10 mg/day is allowed for subjects without active immune disease. Topical, intraocular, intra-articular, intranasal, or inhaled corticosteroids (with minimal systemic absorption) are permitted; and short-term use of corticosteroids for prophylaxis (e.g., contrast allergy) or treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity caused by contact allergens) is permitted.
15) Subjects with serious medical conditions, such as cardiovascular disorders like Grade III or higher abnormal cardiac function (NYHA criteria), ischemic heart disease (such as myocardial infarction or angina pectoris), poorly controlled diabetes mellitus (fasting serum glucose ≥ 10 mmol/L), poorly controlled hypertension (systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg), and ejection fraction < 50% by

echocardiography;

16) QTc interval > 450 msec for males and > 470 msec for females;
17) Abnormal ECG findings and additional risks associated with the use of the investigational product in the opinion of the investigator;
18) Presence of active hepatitis B (HBV DNA ≥ 2000 IU/mL or 10^4 copies/mL) or hepatitis C (positive for hepatitis C antibody and HCV RNA above the lower limit of detection of the assay);
19) Known history of human immunodeficiency virus (HIV)-positive or known history of acquired immunodeficiency syndrome (AIDS);
20) Subjects with a known history of interstitial pneumonia, noninfectious pneumonitis, or highly suspicious of interstitial pneumonia; or subjects with conditions that may interfere with the detection or management of suspected drug-related pulmonary toxicity; and asymptomatic subjects with prior drug-induced or radiation pneumonitis are allowed to be enrolled;
21) Active pulmonary tuberculosis, or previous history of tuberculosis infection but not controlled by treatment;
22) Subjects who have received immunotherapy and experienced ≥ Grade 3 immune-related adverse reactions (ADRs);
23) Use of any active vaccine against infectious diseases (e.g. influenza vaccine, varicella vaccine, etc.) within 4 weeks prior to the first dose or planned to be used during the study;
24) Previous confirmed history of neurological or mental disorders, including epilepsy or dementia;
25) History of definite drug abuse or alcohol abuse within 3 months;
26) Pregnant or lactating women;
27) Participation in other clinical trials within 1 month prior to the first dose;
28) Other factors that may affect the efficacy or safety evaluation of this study in the opinion of the investigator.

4.3 Screening Failure

Screening failure is defined as premature withdrawal of the subject from the study prior to drug administration after signing the ICF. For subjects who fail screening, the original documents should be completed and they should be recorded in the electronic case report form (eCRF) without any further follow-up visit.

Re-examination may be performed and recorded at screening if deemed necessary by the investigator.

4.4 Criteria for Subject Supplementation

Not applicable.

5 Investigational Product

5.1 Administration of Investigational Product

5.1.1 General Information of the Investigational Product

Name: KL-A167 Injection

Dosage form: Injection

Strength: 200 mg (10 mL)/vial

Ingredient: Recombinant humanized anti-PD-L1 monoclonal antibody

Shelf life: 3 years (tentative)

Storage conditions: stored in tightly closed containers, and protected from light at 2-8 ℃

R&D and manufacturing unit: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd

KL-A167 Injection was prepared in a workshop that complies with the conditions of Good Manufacturing Practice (GMP) and passes the test according to the specifications approved by the National Medical Products Administration (NMPA, formerly China Food and Drug Administration (CFDA)). The manufacturing date and expiry date of the drug are provided at the time of use. Please check before use.

5.1.2 Dosage and Administration

The subjects will receive KL-A167 Injection 900 mg as an intravenous infusion on Day 1 of each cycle (one cycle = 14 days). No more than 30 mL will be infused for the first 30 minutes of each cycle, and the total duration of infusion should not be less than 120 minutes. Dosing will be continued until confirmed PD or intolerable toxicity or withdrawal of consent (Note: “Confirmed PD” is defined as the PD confirmed as per irRECIST and the subject has no further potential to obtain clinical benefit as judged by the investigator).

5.1.3 Dose Modification and Discontinuation Criteria

The doses administered in this study will not be reduced or increased.

For subjects who experience drug-related AEs, the KL-A167 injection may be interrupted for up to 12 weeks at the discretion of the investigator and should be discontinued if the event fails to recover to Grade 0-1 or the levels specified in the eligibility criteria within 12 weeks after the last dose. For the determination of “drug-related immune-related adverse events (irAEs)”, firstly, it is necessary to determine whether the AE is drug-related, and, secondly, to determine whether the drug-related AE is immune-related. The irAEs can be determined based on the specific information in Annex 9.

The dosing of subjects will be adjusted based on the occurrence of AEs in the previous period. All AEs will be graded according to NCI CTCAE (V5.0). Table 1 is developed in accordance with the

NCCN Guidelines for the Management of Toxicities Associated with Immunotherapy (V.1, 2020) and is for the information of the investigator only. The management of AEs will be determined by the investigator according to the actual condition of the patient.

Table 1 Reference for the Management of Drug-Related irAEs

Drug-related irAEs	Severity (CTCAE grade)	Clinical Management
Respiratory disorders such as interstitial lung disease	Grade 1	Interrupt treatment until the toxicity resolves
	Grade 2	Interrupt treatment until the toxicity resolves to ≤ Grade 1 and the subject discontinues the steroid therapy. Discontinue treatment if the toxicity has not resolved within 12 weeks after the last dose
	Grade 3-4	Discontinue treatment
Hepatic toxicity	Grade 2 transaminase increased without bilirubin increased	Interrupt treatment until ALT/AST resolves to baseline, and if the subject has taken steroids, resumption of treatment should also be considered when steroids are gradually reduced to doses equivalent to ≤ 10 mg/day of prednisone. Discontinue treatment if the toxicity has not resolved within 12 weeks after the last dose
	Grade 3-4	Discontinue treatment
Colitis/diarrhea	Grade 2-3	Interrupt treatment until the toxicity resolves to ≤ Grade 1 or baseline level; in rare cases, the subject cannot completely discontinue steroids, and resumption of treatment may be considered at doses equivalent to ≤ 10 mg/day of prednisone. Discontinue treatment if the toxicity has not resolved within 12 weeks after the last dose
	Grade 4	Discontinue treatment
Pancreatitis	Symptomatic Grade 2 pancreatitis	Interrupt treatment until the pancreatitis is clinically or radiologically confirmed

Drug-related irAEs	Severity (CTCAE grade)		Clinical Management
			to have disappeared (with or without amylase or lipase increased). Consult with a pancreatic specialist at the same time. Discontinue treatment if the toxicity has not resolved within 12 weeks after the last dose
	Grade 3-4 pancreatitis		Discontinue treatment
Endocrine dysfunction	Diabetes mellitus with diabetic ketoacidosis (DKA)		Interrupt treatment until DKA improves and blood glucose level stabilizes
	Hypothyroidism		Treatment interruption is not required
	Symptomatic hyperthyroidism		Interrupt treatment until clinical symptoms of hyperthyroidism are significantly improved, heart rate returns to normal, and thyroid function is significantly improved
	Primary adrenal insufficiency		Interrupt treatment and resume it if the toxicity resolves to ≤ Grade 1 with appropriate endocrine replacement therapy. Discontinue treatment if the toxicity has not resolved within 12 weeks after the last dose
	Hypophysitis characterized by TSH and/or gonadotropin deficiency, but without symptomatic pituitary swelling		Treatment may be continued in parallel with endocrine replacement therapy
	Hypophysitis with symptoms of pituitary swelling (eg, headache, visual disturbance, and/or neurological dysfunction)		Interrupt treatment until symptoms resolve after steroid therapy; resumption of treatment may be considered after symptoms associated with swelling have resolved
Nervous system disorders	Grade 2-4 encephalitis		Discontinue treatment
	Aseptic meningitis	Grade 1-2	Interrupt treatment until symptoms improve to complete disappearance
		Grade 3-4	Discontinue treatment
	Peripheral neuropathy	Grade 1-2	Interrupt treatment until the toxicity resolves to ≤ Grade 1. Discontinue treatment if the toxicity has not resolved

Drug-related irAEs	Severity (CTCAE grade)		Clinical Management
			within 12 weeks after the last dose
		Grade 3-4	Discontinue treatment
	Guillain-Barre syndrome of all grades		Discontinue treatment
	Grade 2 to 4 myasthenia gravis		Discontinue treatment
Skin and subcutaneous tissue disorders	Maculopapular rash and/or pruritus		Interrupt treatment until the toxicity resolves to ≤ Grade 1. Discontinue treatment if the toxicity has not resolved within 12 weeks after the last dose
	Grade 3-4 bullous dermatitis		Discontinue treatment
Eye disorder	Grade 2		Interrupt treatment until toxicity resolves to ≤ Grade 1 and consult with an ophthalmologist at the same time. Discontinue treatment if the toxicity has not resolved within 12 weeks after the last dose
	Grade 3-4		Discontinue treatment
Myocarditis	Grade 1		Interrupt treatment until the toxicity resolves. Discontinue treatment if the toxicity has not resolved within 12 weeks after the last dose
	Grade 2-4		Discontinue treatment
Other immune-related ADRs	Grade 3		Interrupt treatment until the toxicity resolves to ≤ Grade 1. Discontinue treatment if the toxicity has not resolved within 12 weeks after the last dose
	Grade 4		Discontinue treatment

Notes:

1. For subjects with liver metastases and Grade 2 AST or ALT elevations at baseline, treatment should be discontinued if AST or ALT increases ≥ 50% from baseline and continues for at least 1 week.
2. The study should be discontinued and subject should be withdrawn from the study if a ≥ Grade 3 non-hematologic AE occurs again (the second time) after interruption or no more than 12 consecutive weeks.

5.2 Drug Management

5.2.1 Drug Receipt and Reconciliation

Designated personnel at the study site are responsible for the receipt, storage, dispensing and recovery of the drug, and for making records. Clinical study personnel must ensure that the drug can only be used in this clinical study.

The drugs, packaging and labels used in this study will be provided by Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., and transferred to the study site for use. Relevant documents for drug receipt should be signed by the study site personnel in a timely manner.

The drugs shall be managed by designated personnel, and the drug storage record should be completed by the drug managers, and no drug shall be used after the expiry date. Take appropriate measure to prevent damages caused by fire, theft, heating, mould, insects, and mice. The investigational product should be stored in strict accordance with the storage conditions.

Prior to the start of the study, the study nurse or pharmacist is responsible for preparing the investigational product and completing the drug preparation record form. The study personnel will administer the drug to the subjects according to the study protocol, and the actual medication will be truthfully recorded by the study personnel after administration. All the drugs can only be used for this clinical study and not for any other purposes.

After the end of the study, the study nurse or pharmacist should return the remaining drugs to the drug administrator and complete handover records. The used drug packaging, empty vials and residual liquids should be destroyed at the study site, and those that do not meet the destruction criteria should be uniformly recovered and destroyed by the sponsor. Unused drugs will be uniformly recovered and destroyed by the sponsor.

5.2.2 Packaging and Labeling of Drugs

The packaging and labeling of the investigational product KL-A167 Injection for this study will be provided by Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

The label of the investigational product will be marked with the words “For Clinical Study Use Only”, and will be indicated with the name, clinical trial approval number, strength, batch number, manufacturing date, expiry date, storage conditions, manufacturer, and protocol number.

5.2.3 Product Storage and Shelf Life

KL-A167 Injection should be stored in well-closed containers at 2-8 ℃ and protected from light.

5.2.4 Preparation

Drug Preparation

The contents of the vial should be observed for particulate matter and discoloration prior to dilution. Do not use if particles or discoloration is identified.

- Discard the normal saline at an equivalent volume of the KL-A167 Injection that should be drawn from the 250 mL infusion bag containing 0.9% sodium chloride solution.
- Add a corresponding volume of KL-A167 Injection into the infusion bag.
- Invert the container gently without shaking to ensure adequate mixing of the solution.
- Intravenous infusion will be completed via a medical infusion pump using an infusion set

with an on-line membrane filter (0.2 μM) and the start and end times of dosing will be recorded.

Precautions

1) Administration must be performed with readily available emergency equipment and medicinal products, which must include, but are not limited to, the following emergency equipment and medications: epinephrine, bronchodilators, corticosteroids, antihistamines (intravenous administration), intravenous infusion equipment and devices, oxygen inhalation equipment, etc.
2) Different batches of drug should not be used in a single infusion; it should be ensured that the KL-A167 Injection is transparent without any quality problems such as turbidity or precipitation; it should be ensured that the time from withdrawal of the first bottle of KL-A167 Injection to the end of administration is not more than 24 hours (the prepared drug should be stored at 2-8℃ or at room temperature (25℃ ± 5℃)); mixing with other drugs should be avoided; and intravenous bolus injection should be avoided.
3) The infusion rate should be controlled during the administration of KL-A167: No more than 30 mL will be infused for the first 30 minutes of each cycle, and the total duration of infusion should not be less than 120 minutes.
4) In the event of an infusion reaction, refer to Table 2 for its management. Relevant materials such as infusion devices, remaining drugs, and residual infusion solutions can be retained and tested according to the SOP for the Management of Infusion Reactions.

Table 2 Treatment Modification Guidelines for Infusion Reactions of KL-A167

CTCAE Grade	Modifications
Grade 1 - Mild For transient mild reactions, transfusion interruption and clinical intervention are not recommended.	Slow down the infusion speed by 50% and pay close attention to any worsening symptoms. Give clinical intervention if necessary.
Grade 2 - moderate Interrupt treatment or infusion and give systemic therapy immediately (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic treatment is recommended for ≤ 24 h.	Interrupt the dose of KL-A167, re-administer when the infusion reaction resolves to Grade 0-1 and reduce the infusion speed by 50%, pay close attention to any worsening symptoms during this period, and take appropriate therapeutic interventions according to local medical practice. Interrupt this dose if the infusion reaction does not resolve to Grade 0-1 after 4 h of observation.

CTCAE Grade	Modifications
Grade 3 - Severe Persistent symptoms, e.g. slow response to systemic therapy and infusion interruption; recurrence of symptoms after rapid remission; hospitalization due to complications, etc.	Permanently discontinue the drug and withdraw from the study immediately, and take appropriate therapeutic interventions according to local medical practice.
Grade 4 - Life- threatening and urgent clinical intervention indicated	Subjects with Grade 4 infusion reaction should permanently discontinue the drug and withdraw from the study immediately. Take appropriate intervention according to local medical practices.

5.3 Subject Compliance

The administration of all drugs (including the investigational product) must be recorded in the corresponding section of the subject's original documents and eCRF, and the CRA will review these records to determine the subject's compliance with the study protocol.

5.4 Concomitant Medications

All concomitant medications (including initiation/discontinuation date and purpose of administration) must be recorded in the subject's original document and in the appropriate section of the eCRF.

5.4.1 Use of Drugs Permitted

In general, concomitant medications and treatments necessary for supportive care (e.g., antiemetics, antidiarrheals) and subject's safety are permitted, including all prescription medications, over-the-counter (OTC) drugs, herbal additives, intravenous administration, and fluid replacement, etc. All treatments deemed necessary for the subject's health may be given at the discretion of the investigator. If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be included in the eCRF.

The doses of systemic corticosteroids required for the control of infusion reactions or irAEs must be gradually reduced over at least one month, and immunosuppressive doses (equivalent to ≤ 10 mg/day of prednisone) are discontinued prior to the next dose of the investigational product. Administration of steroids as prophylaxis is allowed for subjects with contrast allergy of diagnostic imaging.

5.4.2 Use of Drugs Prohibited

During the study, the following medications are not permitted: immunosuppressive agents (except for the management of drug-related AEs); systemic corticosteroids at daily doses equivalent to > 10 mg of prednisone (except for drugs for the treatment of drug-related AEs); any concurrent non-protocol-specified anti-tumor therapy (i.e., chemotherapy, hormone therapy, immunotherapy, extensive radiotherapy or radiation therapy for target lesions, or standard of care or study drugs for the treatment

of cancer); palliative radiotherapy for symptom control (except for bone metastases); active vaccines against infectious diseases (e.g., influenza vaccine, varicella vaccine, etc.); and herbal products preparations with anti-tumor effects (including but not limited to: Huazheng Huisheng Tablets, Brucea Javanica Oil Soft Capsules, Zhemu Syrup, Cinobufacini, Kangai Injection, Kanglaite, Zhongjiefeng Injection, Aidi Injection, Awei Huapi Gao, Kang'aipiNG Pills, Xiao'aiping Pills, Pingxiao Capsules, Pingxiao Tablets, Shendan Sanjie Capsules, Ankangxin Capsules, Bosheng Aining, Kanglixin Capsules, and Cidan Capsules).

6 Study Procedures

6.1Screening Visit (Day -14 to Day -1)

6.1.1 Study Education and Requirements for Subjects

During the process of obtaining the ICF from the subjects, the investigator must explain in detail the nature, purpose, procedures, expected duration, potential risks and benefits of the study, and any potential discomforts to each subject during the study. Each subject must be informed that his/her participation in the study is voluntary and that he/she may withdraw from the study and withdraw their informed consent at any time which will not affect his/her rights and interests.

After the basic contents of the study have been explained and the investigator confirms that each subject candidate understands the purpose of the study, each subject that will participate in the study or his/her legal representative should be asked to sign and date the ICF and leave the contact information. Subjects or their legal representatives should carefully read and think over before signing and dating the ICF, and sign the ICF after understanding the course of the study and agreeing to participate in the study, and the investigator should also sign the ICF. The ICF is in duplicate, one to be archived in the State's clinical study facility of drugs and the other to be kept by the subject. Subjects who fail to give informed consent or sign the ICF are not allowed to be enrolled in this study.

6.1.2 Physical Examination at Screening

Subjects will participate in the physical examinations conducted during screening after signing the ICF, and they will be assigned the "screening numbers" in the order in which the ICF is signed.

Screening will be performed within 14 days before dosing to screen out the eligible subjects. Demographic data, medical history, height, weight, histopathological diagnosis, CT/MRI, biomarkers, testing of Epstein-Barr virus DNA copies, vital signs, physical examination, ECOG score, ECG, echocardiography, laboratory tests (hematology, blood chemistry, urinalysis, coagulation, thyroid function, lymphocyte subsets, virological examination, blood pregnancy [for women of childbearing potential only]), AEs, and concomitant medications of subjects will be recorded. Of these, test results of CT/MRI and echocardiography obtained within 28 days before dosing at this hospital are acceptable; if hematology, blood chemistry, urinalysis, and coagulation tests are performed more than

7 days from the first dose, they should be repeated within 7 days to 1 day before dosing; blood pregnancy test results obtained within 72 h before the first dose are acceptable [for women of childbearing potential only]; if vital signs are observed more than 2 days from the first dose, they should be repeated within 2 days before dosing. Re-examination may be performed and recorded at screening if deemed necessary by the investigator. The items to be completed for screening within 14 days before dosing are presented in Table 3.

Table 3 Screening Items

Item	Requirements and Observed Indicators
Demographic data	Date of birth, sex, ethnicity, racial, age, etc.
Height/Weight	/
Medical history	Medical history includes current medical history (especially diagnostic information of tumor), past medical history, medication history, immunization history, allergy history, smoking history, alcohol consumption history, areca nut consumption history, drug abuse history, blood transfusion history, clinical trial history, surgical history, and radiotherapy history, etc.
Histopathological diagnosis	/
CT/MRI ▲	Examination performed mainly in the nasopharynx, head, neck, chest, abdomen, and pelvis
Biomarkers	/
Epstein-Barr virus DNA copy number test	/
Vital signs	Blood pressure, heart rate or pulse, respiratory rate, and temperature
Physical examination	Including skin, mucosa, lymph nodes, head, neck, chest, abdomen, spine/extremities, and nervous system examinations, etc.
ECOG score	Record the score
ECG	Standard 12-lead ECG
Echocardiography	Left ventricular ejection fraction (LVEF)
Hematology	Red blood cell (RBC), hemoglobin (HGB), platelets (PLT), white blood cell (WBC), neutrophil count (NEUT #), lymphocyte count (LYMPH #), etc.
Blood chemistry ●	Albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total bilirubin (TBIL), urea (Urea) or urea nitrogen (BUN), creatinine (Cr), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), triglycerides (TG), total cholesterol (CHO), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), troponin T (TnT), total amylase (AMY), lipase (Lip), blood glucose (GLU), potassium (K^+), sodium (Na^+), chloride (Cl^-), calcium (Ca^{2+}), etc.

Item	Requirements and Observed Indicators
Urinalysis ★	Urine glucose (GLU), ketone body (KET), bilirubin (BIL), urobilinogen (URO), urine protein (PRO), acidity or alkalinity (PH), occult blood (BLO), microscopic red blood cell (JJHCB), microscopic white blood cell (JJBCB), etc.
Coagulation	Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (FIB)
Thyroid function	Thyroid stimulating hormone (TSH), free tri-iodothyronine (FT3) and free thyroxine (FT4)
Lymphocyte subsets test	/
Virological test ◆	Hepatitis B (five items), hepatitis C virus antibody (HCV-Ab), treponema pallidum antibody (TP-Ab), and human immunodeficiency virus antibody (HIV (1 + 2) Ab)
Blood pregnancy	Chorionic gonadotropin (HCG)

▲ CT/MRI: It mainly refers to the examination of nasopharynx, head, neck, chest, abdomen and pelvis. If there is no contraindication, enhanced scan is preferred. The same imaging method is used during the study for the same lesion. Bone scan at screening is performed at the discretion of the investigator.

● Blood chemistry: Troponin T (TnT), total amylase (AMY), lipase (Lip) are not routine safety assessments, and all sites may determine whether tests are necessary at the discretion of the investigator, and if necessary, corresponding surrogates may be used; if not necessary, tests may not be performed.

★ Urinalysis: If microscopic red blood cell (JJHCB) and microscopic white blood cell (JJBCB) cannot be performed, other methods such as dry chemistry can be used, and comments and instructions can be made in the eCRF.

◆ Virological examination: including hepatitis B (five items), hepatitis C virus antibody (HCV-Ab), treponema pallidum antibody (TP-Ab), and human immunodeficiency virus antibody (HIV (1 + 2) Ab). Hepatitis B virus DNA (HBV-DNA) should be tested if hepatitis B surface antigen is positive, and hepatitis C virus RNA (HCV-RNA) should be tested if hepatitis C virus antibody is positive.

6.1.3 Inclusion/Exclusion

Eligibility will be assessed according to the inclusion/exclusion criteria. Eligible subjects will be assigned an "enrollment number" in the order in which they are screened.

6.2 Treatment Visits

6.2.1 Cycle 1 Day 1 Visit

1) Vital signs: within 2 days before dosing and within 1 h after the end of dosing;
2) Immunogenicity blood sampling: within 24 h before dosing;
3) PK blood sampling: within 1 h before dosing and within 30 min after the end of dosing;
4) Dosing;
5) AEs and concomitant medications will be recorded.

6.2.2 Day 1 ±2 of Each Subsequent Cycle

1) Body weight measurement;

2) Vital signs: pre-dose (within 2 days) and within 1 h after the end of dosing;
3) Physical examinations;
4) ECOG score;
5) Laboratory tests: hematology, blood chemistry, urinalysis, coagulation, thyroid function
6) Electrocardiogram;
7) Dose eligibility assessment: AEs in the previous cycle do not meet the criteria for treatment interruption and discontinuation;
8) Immunogenicity blood sampling: within 24 h before dosing;
9) PK blood sampling: within 1 h before dosing and within 30 min after the end of dosing in Cycles 2-5;
10) Dosing;
11) AEs and concomitant medications will be recorded.

During the treatment period, imaging examinations will be performed on the last day of every 6 weeks from the first dose to evaluate the efficacy, with a time window of no more than ± 5 days. Subjects with persistent disease response may undergo imaging assessments every 12 weeks (± 5 days) if 24 months has elapsed after the first dose. Each response assessment should be performed as planned, even in the event of a dose delay. Epstein-Barr virus DNA copy number and lymphocyte subsets were tested at the time of efficacy evaluation.

6.2.3 Withdrawal Visit

Withdrawal Visit should be performed within 7 days after the determination of withdrawal for any reason, and the specific time of withdrawal examination should be determined by the investigator according to the actual situation. If CT/MRI is completed within the first 4 weeks of the withdrawal visit, laboratory tests, ECGs, echocardiography, immunogenicity blood sampling, and blood sampling for Epstein-Barr virus DNA copy number are completed within the first 7 days, they will not be required at this stage.

1) Body weight measurement;
2) CT/MRI;
3) Vital signs;
4) Physical examinations;
5) ECOG score;
6) Laboratory tests: hematology, blood chemistry, urinalysis, coagulation, thyroid function, and lymphocyte subsets;
7) Electrocardiogram;
8) Echocardiography;

9) Epstein-Barr virus DNA copy number test
10) Immunogenicity blood sampling;
11) AEs and concomitant medications will be recorded (if the subject starts a new anti-tumor therapy after leaving the group, concomitant medications, and new AEs after the start of new anti-tumor therapy will not be recorded).

6.3 Safety Follow-up

Follow-up visit will be performed on Day 30 ±5 days after the completion of the withdrawal visit in the form of a hospital visit or telephone follow-up visit based on the specific condition of the subject. Immunogenicity blood sampling will be performed at hospital follow-up visits; otherwise, safety will be followed up via telephone calls.

6.4 Survival Follow-up

Survival follow-up is required for all patients. Survival follow-up will be performed every 30 ± 7 days after the safety follow-up visit by telephone or hospital visit to record the survival of the patient until the patient dies or the subject is lost to follow-up. If the patient is lost to follow-up, the survival cutoff date is the date when the patient is last known to be alive.

6.5 Unscheduled Visits

During the study, considering the safety of the subjects, if a subject experiences an AE or has any laboratory abnormality, the investigator may increase the number of follow-up visits for the subject, i.e. unscheduled visits, as needed. The investigator must accurately record each unscheduled visit of the subject in the unscheduled follow-up section of the subject's original documents and eCRFs.

6.6 Processing and Testing of Biological Samples

6.6.1 Sample Collection

Immunogenicity:

Blood sampling for testing will be performed within 24 h before dosing on Day 1 of each cycle, at the withdrawal visit and follow-up visit (in case of hospital visit).

Biomarkers:

Subjects will be required to have blood drawn at screening. Archival tumor tissues should be provided, otherwise, fresh tumor tissues will be collected for biomarker testing at screening.

PK:

There will be a total of 2 blood sampling time points in each cycle for Cycles 1-5: within 1 h before dosing and within 30 min after the end of dosing on Day 1.

Collection, Processing, Shipment and Storage of Biological Samples:

Specific procedures for blood sampling and blood sample processing for immunogenicity and PK studies are detailed in the Central Laboratory Operations Manual. The transportation of samples

should be undertaken by a professional cold chain logistics company, and the specific operation is detailed in the Central Laboratory Operations Manual.

Specific procedures for blood collection, tumor tissue collection and sample processing for biomarker studies are detailed in the Central Laboratory Operations Manual. The transportation of samples should be undertaken by a professional cold chain logistics company, and the specific operation is detailed in the Central Laboratory Operations Manual.

6.6.2 Sample Testing

In this study, anti-drug antibodies (ADAs) in the blood samples of subjects should be tested before and after dosing, and the neutralizing antibodies (NAbs) analysis should be determined based on the results of the study. The test methods are detailed in the Central Laboratory Operations Manual.

In this study, the expression of sPD-L1 in blood samples of subjects, and the expression of PD-L1 in tumor tissues should be detected. The test methods are detailed in the Central Laboratory Operations Manual.

In this study, the drug concentration of KL-A167 in blood samples should be measured. The test methods are detailed in the Central Laboratory Operations Manual.

6.6.3 Quality Assurance of Sample Testing

Unknown samples should be determined after completion of bioanalytical method validation. Each unknown sample is generally measured once and may be retested if necessary. A new calibration curve should be established for each analytical run of biological samples, and quality control samples at 3 concentrations of low, medium and high levels should be determined concurrently, with multiple samples at each concentration. The number of quality control samples per run should not be less than 5% of the number of unknown samples and not less than 6. In general, the deviation of the determination results of quality control samples should be less than 20%. Up to 33% of the quality control sample results are allowed to be out of limits, but not all at the same concentration. If rejected, the measurement of samples in the analytical run is invalid.

7 Withdrawal and Removal Criteria

7.1 Withdrawal Criteria

7.1.1 Withdrawal at Investigator’s Discretion

If a subject who has been enrolled in the study experiences the following conditions, because of which it becomes inappropriate for the subject to continue the study, the subject will be withdrawn from the study at the discretion of the investigator:

1) Those who are severely allergic to the components contained in this investigational product;
2) Those who experience AEs which make the subject not suitable to continue the study in the opinion of the investigator;

3) Poor compliance and inability to comply with the study requirements during the study;
4) Other circumstances that, in the opinion of the investigator, make the subject not suitable to continue the study.

7.1.2 Withdrawal at Subject's Willing

1) The subject or his/her family member refuses to continue to participate in the clinical study and proposes withdrawal to the physician;
2) Lost to follow-up.

Subjects have the right to withdraw from the study at any stage of the study. In other cases, if subjects are lost to follow-up by no longer taking any drugs or receiving blood sampling but without withdrawing their consents, they are also considered as "withdrawal" or "dropout".

For subjects who withdraw from the study for whatever reason, their safety and efficacy data should be obtained as far as possible. In any event, the reason for withdrawal from the study should be documented in the subject's original documents and eCRF, and all EOT assessments should be performed if the subject is willing and compliant.

7.1.3 Principles for Handling Subject Dropouts

The reason for dropout should be recorded, and all clinical assessments and laboratory tests at the time of withdrawal required in the protocol should be completed as far as possible to ensure the safety of subjects after dropout, and their survival information should still be followed up and collected with the consent of the subjects. The response, tolerability and adverse reactions of the therapeutic drugs will be analyzed with the last test result carried forward as the final result.

7.2 Criteria for Subject Removal

1) Those who have not taken any study drug after enrollment, or have no records of any visits;
2) Combination use of drugs not specified in the protocol, especially those that have significant impact on the results of the study and will affect the judgment of efficacy or safety of the study drug;
3) Other serious violations of the study protocol judged by the principal investigator.

Reasons for removal should be specified, and their original documents should be retained for future audit.

7.3 Lost to Follow-up

Lost to follow-up refers to the situation that the investigator fails to contact the subject using the contact information provided by the subject at different time intervals for multiple times. Any efforts made should be recorded in the documents.

8 Study Assessments

8.1 Efficacy Assessment

8.1.1 Tumor Assessment

According to RECIST 1.1 and irRECIST, imaging tests and tumor size measurements will be performed at each time point specified in the protocol. Tumor scan results will be collected and archived as subject source data. Archival documentation and radiological imaging data of all tumors should be verified with the raw data.

8.1.2 Evaluation of Efficacy

Primary efficacy measure: ORR assessed by the Independent Review Committee using RECIST v1.1. It refers to the fact that objective anti-tumor efficacy is assessed per RECIST v1.1, and BOR would be calculated by taking the number of subjects with CR/PR and dividing it by the total number of subjects.

Secondary efficacy measure: ORR, PFS, DoR, TTR assessed by the investigator per RECIST v1.1 and irRECIST, and OS.

8.1.3 End Time of Data

This study is expected to end 12 months after the first dose of the last subject.

8.2 Safety Evaluation

Safety evaluations will be performed at screening, during the treatment period, and through the Safety Follow-up Visit. Subjects who withdraw prematurely must receive safety evaluation prior to the withdrawal.

Safety observation variables include: AEs, laboratory tests, vital signs, physical examination, ECOG score, ECG, echocardiography, and early withdrawal due to safety or tolerability reasons, etc.

1) Adverse events;
2) Laboratory tests: Hematology, blood chemistry, urinalysis, coagulation, and thyroid function should be determined at different visit phases of the study;
3) Vital signs: Blood pressure, heart rate or pulse, respiratory rate, and body temperature will be observed at different visit phases of the study;
4) Physical examination: Physical examination, including skin, mucosa, lymph nodes, head, neck, chest, abdomen, spine/extremities, neurological examination, etc., should be performed at different visit phases of the study;
5) ECOG score: Subject scores will be recorded at different visit phases of the study;
6) ECG: A 12-lead ECG at rest is required at different visit phases of the study; ECGs may be added at any time if necessary for the safety of subjects throughout the study;
7) Echocardiography: Echocardiography is required at different visit phases of the study.

8.3 Immunogenicity Evaluation

In this study, blood samples should be collected from subjects for testing of anti-drug antibodies (ADAs) in blood samples before and after dosing. The neutralizing antibody analysis will be performed based on the results of the study.

8.4 Biomarker Evaluation

In this study, the expression of sPD-L1 in blood samples of subjects, and the expression of PD-L1 in tumor tissues should be detected.

8.5 Pharmacokinetic Evaluation

C_{max} and C_{min} will be statistically described according to the scheduled blood sampling points.

Population PK analyses may be performed, as appropriate, in combination with plasma concentration data obtained from other clinical trials of KL-A167. PK parameters include C_{max}, C_{min}, T_{max}, $AUC_{0-\infty}$, AUC_{0-t}, $T_{1/2}$, V_{ss}, CL estimated by the population PK model.

8.6 AEs and SAEs

8.6.1 Definition of AE

An AE is defined as any untoward medical event that occurs after a subject receives the investigational product, which may be manifested as symptoms, signs, diseases, or abnormal laboratory finding, but which does not necessarily have to have a causal relationship with this treatment.

8.6.2 Definition of SAE

An SAE is an AE that meets any of the following criteria:

1) results in death;
2) is life-threatening*;

3) requires inpatient hospitalization or prolongation of existing hospitalization;
4) results in persistent or significant disability/incapacity;
5) is congenital anomaly/birth defect;
6) other important medical events. Any medical occurrence that is not immediately life-threatening, fatal, or leading to hospitalization, but may jeopardize the health of the subject or requires medical interventions to prevent one of the above outcomes based on the appropriate medical diagnosis is generally considered a serious AE.

*Note: the term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.6.3 Collection, Recording and Description of AEs/SAEs

8.6.3.1 Determination of AE/SAE Name

The name of an AE should be a medical term and a medical diagnosis should be preferred. That is, if multiple symptoms, signs and laboratory abnormalities can be referred to or classified as the manifestations of one disease or injury, they will be considered as one AE. If a definitive diagnosis is not possible, symptoms/signs will be used; when a diagnosis is later confirmed, the record will be updated to replace the previous symptoms/signs with the diagnosis.

When determining the name of the AE, it should be ensured that each AE name consists of a single event, and that a diagnosis, symptom/sign represents an AE.

Terms such as hospitalization, surgery and death are not AEs per se, while the causes of these conditions need to be recorded as AEs. When the causes of the above-mentioned conditions are not yet determined, the known information, such as hospitalization and death, can be used as the name of the AE and updated and refined in the subsequent follow-up.

8.6.3.2 Severity of the Event

The investigator is required to grade the severity of each AE.

The investigator will assess the AEs with reference to the NCI CTCAE (version 5.0). If the severity of an AE is not clarified in the guidelines, the investigator may assess it according to the general definition of Grade 1 to 5 and in combination with medical judgment. General Grading of AEs:

Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

*Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone and managing money.

**Self-care activities of daily living refer to bathing, dressing and undressing, eating, washing, taking medicine, etc., and not bedridden.

In case of abnormal laboratory values, it should be determined whether there are clinical symptoms and signs, or whether the values are medically significant. Confirmed conditions (e.g. anemia, ALT increased) rather than the abnormal value itself must be reported as an AE.

8.6.3.3 Causality Judgment

The relationship between AEs and the study drug will be classified based on the five criteria for the analysis of AEs into five categories, i.e., “definitely related, probably related, possibly related, unlikely related and not related”, of which “definitely related, probably related, and possibly related” indicate that the AE is related to the study drug.

Definitely related: consistent with the known type of reactions with the suspected drug; consistent with a reasonable chronological order after administration; alleviation or disappearance of the AE after dose reduction or drug withdrawal, and re-occurrence after re-administration.

Probably related: consistent with the known type of reactions with the suspected drug; consistent with a reasonable chronological order after administration; alleviation or disappearance of the AE after dose reduction or drug withdrawal, but the event can also result from subject’s clinical status or other reasons.

Possibly related: consistent with the known type of reactions with the suspected drug; consistent with a reasonable chronological order after administration; alleviation or less manifestation of the AE after dose reduction or drug withdrawal, but the event can be explained by the subject’s clinical status or other reasons.

Unlikely related: not so consistent with the known type of reactions with the suspected drug; not so consistent with a reasonable chronological order after administration; the event can also result from subject’s clinical status or other reasons.

Not related: not consistent with the known type of reactions of the suspected drug; not consistent with a reasonable chronological order after administration; the event can also be explained by subject’s clinical status or other reasons; the event is alleviated or disappears after the clinical symptoms or other reasons are resolved/excluded.

8.6.4 Timeline and Frequency of AE Assessment and Follow-up

AEs should be observed and recorded from the time of signing the ICF until the end of the safety

follow-up visit (if the subject starts a new anti-tumor therapy after withdrawal from the group, newly occurred AEs after that point will not be recorded). The existing AEs should be followed until the event disappears, resolves, or recovers to the level specified in the eligibility criteria, or is stable and no further follow-up is required as considered by the investigator, or initiation of a new anti-tumor therapy, or until lost to follow-up, or death, or the event can be otherwise explained.

8.6.5 End Time of AEs/SAEs

The end time of the AE should be defined as the time that the event disappears, resolves, or recovers to the level specified in the eligibility criteria, or is stable and no further follow-up is required as considered by the investigator, or is reasonably explained. If the end time is not collected due to the death of the subject, and the AE which is not the direct cause of death persists, the end time of the AE should be left blank indicating the status of "ongoing". If the AE is judged to be the direct or primary cause of death, the end time is the death time.

8.6.6 AE Management

8.6.6.1 Records

At each visit, all AEs observed or mentioned by the subject during the study should be accurately recorded by the investigator in the original medical document and entered into the "AEs" page of the eCRF.

The rules to be followed for recording and describing AEs are: 1) Completeness: The description in the original medical record should include, but is not limited to, the basic information of the clinical study and the subject, the use of the study drug, the occurrence of AE, treatment measures taken for the AE, and the action taken with the study drug, outcome of the AE, causality assessment and rationale and concomitant medications; 2) readability: use of abbreviations of medical terms should be avoided to reduce ambiguity.

The contents to be recorded include, but are not limited to:

- AE name;
- Start date and time of onset;
- Severity (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5);
- Whether actions have been taken (Yes, No);
- Dose effect on the study drug (continued, interrupted, discontinued, study drug completed, not applicable);
- Relationship to study drug (definitely related, probably related, possibly related, unlikely related and not related);
- Whether it is a SAE (Yes, No);
- Outcome of AEs;

- End date;
- Whether the subject withdraws from the clinical study due to the AE (Yes, No).

If laboratory test abnormalities are part of a syndrome, then the syndrome or diagnosis (e.g., anaemia) is recorded rather than the laboratory finding (i.e., hemoglobin decreased).

The investigator should take appropriate measures to ensure the safety of the subjects according to the AEs; the institution should ensure the supply of relevant rescue equipment and drugs to ensure that appropriate treatment can be given in case of emergency.

8.6.7 Management of SAEs

8.6.7.1 Reporting of SAEs

In case of SAEs, the investigator should immediately take appropriate and active rescue and protective measures for the subjects, and may decide whether to discontinue the study based on patients' conditions. Any SAE (whether related to study drug or not) occurring during the study should be completed in the Serious Adverse Event Report Form by the investigator and reported to the sponsor within 24 h of awareness. The sponsor's e-mail address is sae@kelun.com.

For reports involving death events, the investigator should provide the sponsor and the EC with other required information, such as the necropsy report and the final medical report.

The sponsor should promptly report any suspected unexpected serious adverse reactions (SUSARs) to all investigators participating in the clinical trial, as well as study sites and EC; the sponsor should report SUSARs to drug regulatory authorities and health authorities.

The investigator should read and sign relevant safety information of the clinical study provided by the sponsor in a timely manner, then consider whether the treatment for the subject should be adjusted as appropriate, communicate with the subject as soon as possible when necessary, and report the SUSARs provided by the sponsor to the ethics committee and the study sites.

8.6.7.4 Follow-up of SAEs

All SAEs should be followed until the event disappears, resolves, or recovers to the level specified in the eligibility criteria as judged by the investigator, or is stable and no further follow-up is required as considered by the investigator, or initiation of a new anti-tumor therapy, or until lost to follow-up, or death, or the event can be otherwise explained. The frequency of follow-up will be determined by the investigator according to the specific situation of SAEs.

8.6.7.5 Determination of Expectedness of SAEs

The assessment of expectedness should be based on serious adverse reactions observed in clinical studies, and the determination of expectedness of SAEs occurring during the study in subsequent clinical studies will be based on the expected serious adverse reactions listed in the section of the Reference Safety Information in the Investigator's Brochure (see the most recent version of the

Investigator's Brochure for details of the drug Reference Safety Information).

8.6.8 Progressive Disease

Unequivocal symptoms or signs of tumor progression should not be recorded as AEs (with a clear diagnostic rationale) unless they are more severe than expected or are considered by the investigator to be related to study drug administration or study procedures. If a new primary malignancy occurs, such an event should be reported as an SAE.

All deaths during the study should be reported as SAEs (including deaths due to PD).

8.6.9 Hospitalization

In this clinical study, the AEs that lead to hospitalization or prolongation of existing hospitalization should be considered as SAEs (except for hospitalization due to PD). Any first hospitalization to a medical facility (even if less than 24 hours) meets this criterion. Hospitalization also includes in-hospital transfer to an emergency/intensive care unit (e.g., from a medical ward to a cardiac care unit).

Hospitalization does not include the following:

- Admitted by routine emergency room
- Day surgery (e.g., outpatient/day/ambulatory surgery) (observation in outpatient departments for less than 24 hours)
- Nursing homes
- Rehabilitation facilities
- Hospice care facilities (e.g. nursing homes)

Hospitalization or prolongation of hospitalization not associated with worsening of the AE is not an SAE per se, e.g.:

- Hospitalization due to a pre-existing disease that does not become worsened without the onset of any new AEs (e.g., hospitalization due to laboratory abnormalities that occur prior to the study and still persist);
- Hospitalization due to administrative reasons (e.g., annual routine physical examination);
- On-study hospitalization as specified in the protocol (e.g., protocol-specified procedures);
- Elective hospitalization unrelated to worsening of the AEs (e.g. elective cosmetic surgery);
- Pre-scheduled treatment or surgery which should be recorded in the protocol and/or in the subject's baseline data;
- Hospitalization only for use of blood products.

Diagnostic or therapeutic invasive (e.g., surgery) and non-invasive procedures should not be reported as AEs. However, disease conditions leading to the operation of this procedure should be reported as AEs if they meet the definition of AEs. For example, acute appendicitis that occurs during the reporting period of an AE should be reported as an AE, therefore, the appendectomy performed for

the disease should be recorded as the treatment for this AE.

8.6.10 Pregnancy Report

Pregnancy of a female subject or partner of a male subject during the study should be reported to Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. and the EC of the study site within 24 hours of awareness.

Female subjects who become pregnant are required to be withdrawn from the study immediately, and will be recorded, reported, and followed up in accordance with the SOPs of the clinical study site; male subjects are not required to be withdrawn from the study after their partners become pregnant; however, the pregnancy of their partners should be recorded, reported and followed up in the same manner as pregnant female subjects.

Pregnancy per se will not be considered as an AE or SAE, but any of the complicated conditions that occur during pregnancy will be recorded, reported, and followed up as the "SAE" in accordance with the provisions of the protocol. Complicated conditions include: spontaneous abortion (including threatened abortion, inevitable abortion, complete abortion, incomplete abortion, habitual abortion), stillbirth, fetal/neonatal congenital anomaly, or deformity; and termination of pregnancy for medical reasons.

9 Statistical Considerations

9.1 General Statistical Considerations

The primary objective of this study is to evaluate the efficacy and safety of KL-A167 injection in subjects with recurrent or metastatic NPC. All statistical programming will be performed using SAS. The efficacy results are mainly statistically inferential, and the safety results are mainly described statistically.

9.2 Sample Size Estimation

The assumed ORR of KL-A167 Injection in the treatment of recurrent or metastatic NPC could reach 26%. The investigational product will be considered effective if the lower limit of the 95% confidence interval (CI) for ORR is not less than 15%. Based on the 95% CI of ORR estimated by the Clopper-Pearson method, the drug can be considered effective based on a statistical power of 90% obtained for 139 samples at a level where type 1 error is controlled to two-sided 0.05. A total of approximately 153 subjects will be required considering a dropout rate of 10%.

9.3 Populations for Analyses

(1) Full analysis set (FAS): all subjects who have received at least 1 dose of investigational product. The FAS will be used for baseline and efficacy analyses.

(2) Safety set (SS): all subjects who have received at least 1 dose of investigational product and have safety evaluation variables. SS will be used for safety analysis.

(3) Per protocol set (PPS): subjects who complete all doses of investigational product required by the protocol, with the primary endpoints available and without major protocol violations. The PPS will be used for supplementary analysis of efficacy data.

(4) PK concentration set (PKCS): subjects who have received at least one dose of the investigational product and have at least one valid post-dose component concentration data. The PKCS is used to describe the PK concentration data and estimate PK parameters in subjects.

9.4 Statistical Analysis

9.4.1 Efficacy Analysis

Definitions of efficacy variables:

1) Objective response rate (ORR): proportion of subjects with best response of CR or PR among all treated subjects.
2) Progression-free survival (PFS): the time from the start of the first day of dosing to the onset of PD or death.
3) Overall survival (OS): the time from the start of enrollment to death due to any cause.
4) Disease control rate (DCR): proportion of all treated subjects with best response of CR, PR, or SD.
5) Duration of tumor response (DOR): the time from the first CR or PR to PD for subjects who achieve CR or PR.
6) Time to response (TTR): the time from the first dose of the subject to the first documented CR or PR.

The 95% CI of ORR will be estimated using the Clopper-Pearson method, and the drug can be considered effective when the lower limit of the CI of the subject is not less than 15%. The Kaplan-Meier method will be used to estimate the median and 95% CIs of PFS, OS, DOR, TTR and corresponding survival curves will be plotted.

9.4.2 Safety Analysis

Based on the safety analysis set (SAS), safety variables will be assessed using the SAS. Safety variables include AEs, physical examinations, vital signs, ECOG score, laboratory tests, ECGs, echocardiography, and early withdrawal due to safety or tolerability reasons, etc. The entire test items of physical examinations, laboratory tests, ECGs, and echocardiograms will be listed in a pre- and post-treatment cross-tabulation (based on normal ranges and clinical significance as judged by the investigator). Changes in vital signs and ECOG scores over time will be listed. Abnormal tests after treatment will be presented in lists. All AEs occurring during this clinical study will be coded using MedDRA, and the number of subjects and number of events for AEs will be listed in detail by SOC/PT classification.

9.4.3 Immunogenicity Analysis

Immunogenicity assessment data will be presented according to the categories listed below. These data include number and percentage of subjects with positive ADA test results at baseline, number and percentage of subjects with at least one positive ADA test result at any time point after the first dose, number and percentage of subjects with treatment-induced positive ADA test results at any time point after the first dose, and number and percentage of subjects with treatment-enhanced positive ADA test results at any time point after the first dose.

9.4.4 PK Data Analysis

The plasma concentration data of KL-A167 obtained in this study will be subjected to descriptive statistical analysis.

Population PK analyses may be performed, as appropriate, in combination with plasma concentration data obtained from other clinical trials of KL-A167. PK parameters mainly include C_{max}, C_{min}, T_{max}, $AUC_{0-\infty}$, AUC_{0-t}, $t_{1/2}$, V_{ss}, CL estimated by the population PK model.

9.4.5 Exploratory Analyses

The expression levels and distribution of PD-L1 and sPD-L1 will be analyzed descriptively, and their potential relationship with efficacy will be explored. The analysis will be performed based on data collection.

9.5 Data Monitoring Committee (DMC)

A DMC will be established in this study, as appropriate, to interpret, judge and make recommendations on AEs during the trial and the main results of the main analysis. The DMC consists of experts in relevant specialties, including experts in relevant areas of clinical trial indications, experts in SAEs, experts related to the judgment of the main results of clinical trials, biostatisticians, and experts in ethical aspects.

10 Supporting Documents and Operational Considerations

10.1 Regulations, Ethics and Regulatory Considerations of Clinical Trials

10.1.1 Process of Informed Consent

Each subject should sign the ICF before participating in the study, as detailed in Section 6.1.1.

10.1.2 Study Discontinuation

Study discontinuation means that the clinical study has not been ended according to the protocol, and all the studies have been stopped during the study. The main purpose of discontinuation is to protect subjects' rights and interests, ensure the quality of the study and avoid unnecessary economic losses.

1) If serious safety issues occur during the study, the study should be discontinued in a timely manner;
2) The clinical study protocol is found with major errors in the study, and it is difficult to

evaluate the drug safety, or an important deviation occurs in the implementation of a well-designed protocol, and then it is difficult to evaluate the drug safety if it continues;

3) Discontinuation requested by the sponsor (e.g., reasons of funding, management, etc.);
4) Withdrawal of the study is ordered by the National Medical Products Administration for some reason.

10.1.3 Confidentiality and Privacy

This study will only collect and process data from subjects that the use of which are limited to the evaluation of efficacy, safety, quality, and clinical application of the investigational product.

The confidentiality of these data will be sufficiently protected and the relevant laws and regulations protecting the privacy of subjects will be followed when the data are collected and used.

10.1.4 Key Roles and Study Management

The sponsor is responsible for providing the study site with information such as the study-related Investigator's Brochure and research funding, qualified investigational products and study materials (including copies of the sponsor's business license, drug production license, Good Manufacturing Practice (GMP) certificate, original certificate of analysis, etc.) free of charge. And the sponsor and the investigator will jointly formulate the study protocol, which will be mutually approved by the two parties. This study will be conducted by the investigator according to the protocol and in accordance with the current national regulations.

The study site should strictly keep all information provided by the sponsor confidential, and other study participants and EC should also be required to take the same confidentiality measures. Information provided to the study site must not be disclosed to others without written permission from the sponsor.

10.1.5 Safety Oversight

The doctors and nurses of the study site will be responsible for the monitoring of AEs throughout the study. Subjects who experience any discomfort during the study can contact their doctors promptly.

10.1.6 Clinical Trial Monitoring

Study Monitoring

The CRA should monitor the conduct of the study in accordance with the requirements of GCP, including but not limited to:

- Confirm before initiation of the study that the study site has appropriate conditions, including staffing and training, a well-equipped and well-functioning laboratory, various study-related testing capacities, a sufficient estimated number of subjects;
- Monitor the implementation of protocol by the investigator during the study, and confirm that the informed consents are obtained from all subjects before initiation of the study,

ensure subject's enrollment rate and progress of the study, and verify the eligibility of enrolled subjects;

- Confirm that all AEs are recorded, and SAEs are reported and recorded within the specified time;
- Clearly and truthfully record any visit, test and examination unaccomplished by the investigator, and verify that corrections are made for the errors and omissions;
- Verify whether the investigational product is supplied, stored, dispensed, used and retrieved in accordance with relevant regulations and recorded accordingly.

Study Auditing and Inspecting

Audits will be conducted by relevant personnel not directly involved in the study and inspections will be conducted by drug regulatory authorities. When audits and inspections are conducted by relevant personnel, the research facility must provide the materials to be examined in a timely manner.

10.1.7 Quality Assurance and Quality Control

All investigators must be trained in the protocol before the initiation of the study. The protocol and relevant SOPs must be strictly followed during the study. The project leader should carefully review the records and check the data. The sponsor should send qualified CRAs to supervise the study process and reconcile the study data. The following requirements need to be met:

- The original document must comply with China GCP requirements;
- Laboratory results must be accurate, reliable and complete;
- All observations and findings should be verified to ensure the reliability of the data;
- All staff participating in the study should strictly comply with the provisions of the protocol and follow the procedures, and the records should not be changed arbitrarily;
- The designated statistician is responsible for the overall statistical processing of the data;
- After the end of the study, the eCRFs will be recorded on disk and placed in the custody of the National Drug Clinical Trial Institute of the study site.

10.1.8 Data Processing and Record Retention

10.1.8.1 Data Collection

All prespecified subject information (original laboratory test reports are uniformly pasted in the specified locations of the original medical records) will be collected by trained clinical investigators in accordance with the protocol and SOPs using the original medical records in a standardized, complete and accurate manner, and the privacy of the subjects should be protected during the collection process. The investigator reviews all data collected to ensure that all data are recorded in a timely, accurate and complete manner, and is responsible for the authenticity of the data. If an AE occurs in the study, the investigator should confirm that all AEs are recorded in a standardized manner,

and SAEs are reported and recorded as required. Data and documents should be safely and completely stored during the study, and the data and related documents should be archived as agreed upon after the end of the study.

10.1.8.2 Data Entry and Monitoring

EDC is used for data management in this study. According to the original medical records, study data for all subjects must be entered into the designated EDC system in a complete, accurate, and timely manner, including dropouts.

10.1.8.3 Data Management

Data management plan (DMP) is a detailed specification of clinical trial data management tasks. Data manager should comprehensively describe the data management process, each step of data management and quality assurance measures in accordance with the clinical trial protocol. This document is a dynamic document, which can be modified and updated according to the actual situation during the study, and can be implemented only after approval by the sponsor. The entire data management process shall be carried out in accordance with the relevant provisions of the DMP.

The main steps or contents of data management include, but are not limited to, the following:

eCRF design: The data manager should strictly design the draft eCRF according to the protocol, pay attention to the protection of subject privacy when designing the eCRFs, and the final eCRF should be reviewed and approved by the sponsor. Annotated eCRF should be generated when eCRFs are constructed.

Edit check: The data manager shall design and test the edit program according to the characteristics of the EDC system and according to the actual requirements of the project. The edit check can be performed in two ways: automatic edit check and manual edit check. After the edit check configuration is completed, the data management unit and the sponsor shall jointly conduct user acceptance testing (UAT).

eCRF completion guidelines: The eCRF completion guidelines are completion rules to help the study personnel correctly fill in the eCRF, with designation of the correct use of the EDC system, and the correct method of data completion and change, etc. The description of this guideline should be legible.

Database on-line: When the eCRF, edit check and database design and development are completed, the data manager shall confirm that all design and development steps have successfully passed the user test, and confirm that all design documents and test documents are finally signed and archived. When everything is ready, the EDC system is ready to go online.

Data collection: The study personnel should collect subject data in accordance with GCP and protocol requirements. The investigator or his/her authorized CRC should log into the EDC through

an independent account, and complete the subject data entry sequentially according to the guidance/requirements of the completion guidelines. All data should be entered accurately, timely, completely in a standardized manner. During the entry process, the queries issued by the system shall be resolved/answered in a timely manner.

Source data verification and confirmation: The consistency of the trial collection data and source documents will be checked by the CRA and marked and documented within the EDC system. If inconsistencies are identified, data queries should be issued based on the EDC and resolved by the investigator or his/her authorized CRC.

Data verification: Data manager, medical monitors, etc., should conduct data verification in a timely manner according to the work plan established in advance. Relevant queries shall be issued in response to the problems found in the data verification, and the investigator or his/her authorized CRC shall answer the queries. After the query issuer confirms that the query is resolved, the query could be closed. If problem persists, the query may be reissued until the problem is completely resolved. Error data should be corrected during data cleaning, but the correction must be completed by query response.

Medical coding: Standard dictionaries are recommended for the coding of AEs and concomitant medicines etc. MedDRA is recommended for medical coding of AEs in this study. For prior and concomitant medications, WHO Drug Dictionary is recommended for coding.

System change control: If the EDC is changed during the study due to protocol amendment, design defects or errors in eCRFs, the change process should be strictly controlled, and the change contents, start and end dates shall be recorded in detail, and the original data shall be ensured to be non-destructive. The changed system shall be fully tested, and all system users shall be informed in a timely and appropriate way when re-online.

External data management: A draft external data transfer agreement (DTA) will be written by the data management unit, and specific technical requirements will be made for the structure, content, transmission mode, transmission time and workflow of external data. The sponsor and the biological sample testing unit shall review and confirm the DTA. The biological sample testing unit shall complete the secure transmission of external data according to the provisions of the DTA, and the data manager shall verify the external data in a timely manner. If problems are found in the verification, they should be confirmed with the biological sample testing unit in a timely manner, and if necessary, data may be required to be retransmitted.

Data blind review: Before the clinical trial database is locked, the investigator, sponsor, data manager and statistician should be organized to jointly review the unresolved issues in the data under the blinded state, and divide the statistical analysis population according to the clinical trial protocol, and

verify the report and handling records of SAEs.

Database locking and unlocking: After the data manager has established the database lock list, and the investigator, sponsor, data manager, statistician, etc. jointly confirm that all contents in the lock list are completed, the database lock approval document shall be signed, and the data management unit shall complete the database lock, and recover the data editing authorization of the database. If data issues are identified after database lock, the potential impact of these data errors on safety and efficacy analyses should be carefully considered and evaluated. Not all data errors found must be corrected in the database itself, and data errors can also be recorded in the statistical analysis report and clinical report documentation. If the database must be unlocked, the signature and confirmation must be completed by the principal investigator, sponsor, data manager and statistician. After the issue is resolved, the database lock is completed again according to the database lock process.

Data management report (DMR): After database lock, a DMR will be written by the data manager, which fully and detailedly describes the contents related to the data management process, operating practices and quality of management, and the DMR shall be reviewed and approved by the sponsor.

Data backup: The database should be backed up in a timely manner throughout the data management process.

Document archiving: After the completion of the clinical trial, documents during the study should be archived.

10.1.9 Protocol Violations

A protocol violation is defined as any noncompliance with the requirements of the clinical study protocol, the GCP, or the operating manual. Noncompliance may arise from subjects, the investigator, or the staff of the study site. Corrective actions should be taken to address the violations and completed in a timely manner.

10.1.10 Study Results Publication and Data Sharing Policy

This study is a clinical study of the drug, and the study data are for use only at the time of application of the drug.

Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. and the CRA will have access to the study data for monitoring purposes. When relevant personnel not directly involved in the conduct of the study need to audit the data or the data are inspected by drug regulatory authorities, the study site should provide the data in a timely manner.

Regarding the publication of the results of this study, whether in part or in whole, consent should be obtained from Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. The investigator are not allowed to publish any data and information related to the study without the consent from Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

10.2 History Record of Protocol Amendments

- If revisions are warranted after the protocol has been approved by the EC, a statement of protocol amendments should be prepared with signature of the principal investigator, and the protocol can only be revised after obtaining the approval from the sponsor.
- Any protocol amendment should not be implemented without the review by or file with the EC.
- Revision record:

Version change: upgraded from V1.0/26 Nov, 2018 to V1.1/25 Dec, 2018		
Revision Location	**Revision Points**	**Reason for Revision**
Exclusion Criteria	An exclusion criterion is added: 1) Subjects with locally advanced disease will not be screened if they can receive radical treatment such as surgery, radical radiotherapy, or radical chemoradiotherapy;	Revised based on ethical review comments.
Version change: upgraded from V1.1/25 Dec, 2018 to V2.0/10 Apr, 2019		
Revision Location	**Revision Points**	**Reason for Revision**
Summary and full text	Revisions to sample size, partial eligibility criteria, and biomarker testing are mainly made.	Revised based on comments from the protocol seminar.
Version change: upgraded from V2.0/10 Apr, 2019 to V3.0/22 Mar, 2021		
Revision Location	**Revision Points**	**Reason for Revision**
Summary and full text	The secondary objective “Evaluation of biomarkers” is changed to an exploratory objective.	Only biomarkers with strong correlation with efficacy reported in the literature are retained to explore their relationship to efficacy.

11 References

[4] LIN Cheng, CHEN Xiong, LIU Jingnan, et al. Advances of PD-1/PD-L1 Signaling Pathway in Immune Escape and Treatment for Non-small Cell Lung Cancer [J]. Chinese Journal of Lung Cancer, 2014, 17 (10): 734-740.

Appendices

Annex 1: Principal Study Institution and Study Participants

Project Name	A Phase 2 Clinical Study To Evaluate the Efficacy and Safety of KL-A167 Injection in Patients with Recurrent or Metastatic NPC
Clinical Study Director	SHI Yuankai Cancer Hospital Chinese Academy of Medical Sciences Address, Postcode: No. 17 Panjiayuan Nanli, Chaoyang District, Beijing 100021 Tel: (010) 87788268 Email：syuankaipumc@126.com
Sponsor's Director	QING Yan Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd Address and Postcode: No. 666, 2nd Section, Xinhua Avenue, Haixia Industrial Park, Wenjiang District, Chengdu, 611130 Tel: 028-67255480 Email：qingyan@kelun.com

Annex 2: Abbreviation

ADA	Anti-drug antibody
ADCC	Antibody dependent cell-mediated cytotoxicity
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMY	Amylase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BIL	Bilirubin
BLO	Occult blood
BOR	Best overall response
BUN	Blood urea nitrogen
CAR-T	Chimeric T cell receptor
CCR	Creatinine clearance rate
CFDA	China Food and Drug Administration
CHO	Chinese hamster ovary
CHO	Cholesterol
CK	Creatine kinase
CK-MB	Creatine kinase MB
C_{max}	Maximum observed serum or plasma concentration
Cr	Creatinine
CR	Complete response
CRC	Clinical research coordinator
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
CTP	Clinical trial protocol
DCR	Disease control rate
DMC	Data Monitoring Committee
DMP	Data management plan
DMR	Data management report
DNA	Deoxyribonucleic acid
DOR	Duration of response
eCRF	Electronic case report form

EDC	Electronic data capture
GCP	Good Clinical Practice
GGT	Glutamyl transpeptidase
GLU	Glucose
GMP	Good Manufacture Practice
EBER	Epstein–Barr virus-encoded small RNA
EBV	Epstein-Barr Virus
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
FIB	Fibrinogen
FT3	Free triiodothyronine
FT4	Free thyroxine
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCG	Human chorionic gonadotrophin
HCV	Hepatitis C Virus
HDL	High-density lipoprotein
HGB	Hemoglobin
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio
irRECIST	Immune related Response evaluation criteria in solid tumors
ITSM	Immunoreceptor tyrosine-based switch motif
KET	Ketone body
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
Lip	Lipase
LYMPH#	Lymphocyte
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MTD	Maximum tolerated dose
NOAEL	No observed adverse effect level
NPC	Nasopharyngeal carcinoma
NSAID	Non-steroidal anti-inflammatory drug
NEUT#	Neutrophil count

NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression‑free survival
pH	Hydrogen-ion concentration - acid
PI3K	Phosphatidyl inositol-3-kinase
PKB/AKB	Protein kinase B
PKC	Protein Kinase C
PKCS	Pharmacokinetics concentration set
PLT	Platelet
PPS	Per protocol set
PR	Partial response
PRO	Urine Protein
PT	Prothrombin time
PV	Pharmacovigilance
QTc	QT interval corrected for heart rate
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RO	Receptor occupancy
SAE	Serious adverse event
SAS	Statistical Analysis System
SHP-2	Src homology 2 domain-containing pro-tein tyrosine phosphatase 2
SLE	Systemic lupus erythematosus
SOP	Standard operating procedure
sPD-L1	Soluble programmed death ligand-1
SS	Safety set
TBIL	Total bilirubin
TCR	T cell antigen receptor
TEN	Toxic epidermal necrolysis
TG	Triglyceride
TMB	Tumor mutation burden
TnT	Troponin T

TP-Ab	Treponema pallidum antibody
TSH	Thyroid-stimulating hormone
TT	Thrombin time
TTR	Time to response
ULN	Upper limit of normal
URO	Urobilinogen
WBC	White blood cell
WHO	World Health Organization
ZAP70	Zeta-chain-associated protein kinase 70

Annex 3: Response Evaluation Criteria in Solid Tumors RECIST Version 1.1

1. Measurability of tumour at baseline

1.1 Definitions

At baseline, tumour lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumour 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 (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a 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). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:.

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques 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.
- Blastic bone lesions are non-measurable.

Cystic lesions:.

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:.

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by methods of measurements

1.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. 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.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the

assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. Tumour response evaluation

2.1 Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is

the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2.2 Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm ×30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these

lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3 Response criteria

2.3.1 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 diameters.

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.

2.3.2 Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become ‘too small to measure’. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being ‘too small to measure’. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the

retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in ‘volume’ (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from ‘trace’ to ‘large’, an increase in lymphangitic disease from localised to widespread, or may be described in protocols as ‘sufficient to require a change in therapy’. If ‘unequivocal progression’ is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient’s brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression

(particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

   If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

   If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

   If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4 Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

2.4.1 Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table a on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table b is to be used.

Table a Time point response: patients with target (+/–non-target) disease.

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

Target lesions	Non-target lesions	New lesions	Overall response
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

CR= complete response，PR= partial response，SD= stable disease，PD= progressive disease，NE=inevaluable

Table b Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR= complete response，PD= progressive disease，NE= inevaluable

*Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3 Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent

assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table c.

Table c Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD，PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR= complete response，PR= partial response，SD= stable disease，PD= progressive disease，

NE= inevaluable

a：If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables a-c.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.5 Frequency of tumour re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For

example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6 Confirmatory measurement/duration of response

2.6.1 Confirmation

In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

Annex 4: Immune-Related Response Evaluation Criteria in Solid Tumors (irRECIST)

RECIST v1.1 evaluation criteria are defective in oncology-targeted immunotherapy. The use of RECIST 1.1 in immunotherapy trials can lead to premature declaration of progressive disease (PD) in cases where treatment effect has not been adequately demonstrated. The importance of the "fulminant effect" — the pseudoprogression effect within the outbreak window is also ignored in RECIST.

Immune-related response criteria (irRC) have been published based on WHO criteria to better assess the effects of immunotherapeutic agents. Accordingly, we present irRECIST based on RECIST v1.1 evaluation criteria, irRC, and findings from Nishino et al., 2013. Our objective is to define criteria for better acquisition of anti-tumor activity and to reduce ambiguity of irRC criteria.

irRC and WHO Criteria	**Modification and Clarification of irRECIST**	**Rationale for Modification**
At baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPDs) is calculated for all index lesions (5 lesions per organ, up to 10 visceral lesions, and 5 skin index lesions).	**1.0 Baseline: definition of measurable lesions and selection of target lesions** Definitions as defined in RECIST v1.1 evaluation criteria are followed. Measurable disease must be accurately measured in at least one dimension with a minimum size of: ● For non-nodal lesions, CT or MRI scan shows a longest diameter of 10 mm (or not less than twice the slice thickness), and for nodal lesions, ≥ 15 mm in the short axis ● 10 mm caliper measurement by clinical examination ● 20 mm by chest X-ray	Up to 5 target lesions may be selected at baseline. Lesions will be measured in one dimension. The minimum target lesion size at baseline in irRECIST is consistent with that in the RECIST v1.1 evaluation criteria, as described by Nishino et al., 2013.
WHO 5.1.2 Non-measurable disease Non-measurable diseases can take many forms and only a few diseases are mentioned as examples: 1、Lymphatic pulmonary metastases. 2、Skin involvement in breast cancer.	**1.1. Baseline: definition of non-measurable lesions** Non-target lesions, as defined in RECIST v1.1 evaluation criteria, include: ● Measurable lesions not selected as target lesions ● All sites of non-measurable disease, e.g., the mass is too small to measure because its longest uninterrupted diameter is < 10 mm (or < twice the	Although non-target lesions are not clearly defined in the irRC, the irRC is derived from WHO criteria and indicates that non-target lesions are defined based on this criterion. Further clarification is consistent with that defined in the RECIST v1.1 evaluation criteria.

irRC and WHO Criteria	Modification and Clarification of irRECIST	Rationale for Modification
3、Abdominal mass, palpable but not measured.	thickness of the axial section), i.e., the longest vertical diameter is ≥ 10 mm and < 15 mm. ● Other types of lesions are identified as representative of tumor tissue but are difficult to measure in a reproducible manner. These lesions include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusion, ascites, mastitic diseases, cutaneous lymphangitis/pulmonary lymphangitis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.	
Not specified.	**1.2 Baseline: Lymph Node Target and Non-Target Lesion Definitions** Definitions as defined in RECIST v1.1 evaluation criteria are followed.	There is no change in the definition of target and non-target lesions in lymph nodes as assessed by RECIST v1.1.
Not specified.	**1.3 Baseline: Non-Target Lesion Selection** All lesions or sites of disease that are 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.	Consistent with RECIST v1.1 criteria, all malignant lesions should be selected at baseline. For excess measurable lesions and all truly non-measurable lesions, they should be selected as non-target lesions at baseline and followed up at subsequent timepoints.
Not specified.	**1.4 Baseline: bone lesions** Definitions as defined in RECIST v1.1 evaluation criteria are followed. Acute bone lesions will not be selected as target lesions regardless of imaging modality. Lesions of lytic or mixed lytic blast cells with ≥ 10 mm measurable soft tissue components may be selected as target lesions.	Bone lesions will be managed in the same way as in RECIST v1.1 evaluation criteria.
Not specified.	**1.5 Baseline: brain lesions** Brain lesions detected by brain scan can be	Brain lesions may be selected as target or non-target lesions

irRC and WHO Criteria	Modification and Clarification of irRECIST	Rationale for Modification
	considered as target or non-target lesions.	at baseline based on protocol definitions, indications, and study design.
Not specified.	**1.6 Baseline: cystic and necrotizing lesions as target lesions** Some cystic or necrotizing lesions may be selected as target lesions. The longest diameter of such lesions will be added to the total mutation tumor burden (TMTB) measured for all target lesions at baseline. If other lesions with non-liquid/non-necrotizing portions are present, they should be preferred.	Tumor tissue viability is not added to the RECIST v1.1 evaluation and is transferred to irRECIST.
Not specified.	**1.7 Baseline: lesions with prior local therapy** During target lesion selection, the radiologist will consider information on anatomical sites of prior intervention (e.g., prior irradiation, RF ablation, TACE, surgery, etc.). Lesions with prior intervention will not be selected as target lesions unless PD has been demonstrated.	In order to minimize site-to-site differences, both the investigator and the independent reviewer must have access to information on prior interventions.
Not specified.	**1.8 Baseline: no disease at baseline** If the patient has no measurable and non-measurable disease at baseline, the radiologist will designate "no disease"(irND) as the overall tumor assessment at any available follow-up time point, unless new measurable disease is identified and TMTB can be added.	The irND is a valid assessment in a study using adjuvant therapy, where the protocol and study design may include subjects without visible disease. This is not addressed in any previous immune response-related criteria, but it needs to be included to allow for an accurate assessment of these subjects.
At each subsequent tumor assessment, the SPD of index lesions and new measurable lesions (≥ 5 × 5 mm; up to 5	**2.0 Follow-up: recording of measurements of target lesions and new measurable lesions** The longest diameter of non-nodal target	According to Nishino et al., 2013, the measurement will be performed using one dimension. At follow-up,

irRC and WHO Criteria	Modification and Clarification of irRECIST	Rationale for Modification
new lesions per organ: 5 new skin lesions and 10 visceral lesions) will be added to provide TMTB.	lesions and new non-nodal measurable lesions, as well as the short axis of nodal target lesions and new nodal measurable lesions, will be recorded. These measurements determine the total mutation tumor burden (TMTB) measured at follow-up.	measurements of all measured lesions (target lesions selected at baseline and new measurable lesions) will be combined into the TMTB.
	2.1 Follow-up: definition of new measurable lesions When selected as a new measurable lesion (2 lesions per organ, ≤ 5 lesions in total at each time point), the new lesion must meet the criteria for baseline target lesion selection and meet the same requirements for a new measurable lymph node, i.e., a minimum of 10 mm in the long axis and a minimum of 15 mm in the short axis. Priority should be given to new measurable lesions based on size and the largest lesion should be selected as the new measurable lesion.	Up to 5 new measurable lesions of at least 10 mm per lesion are recommended instead of 10 new measurable lesions recommended by the irRC criteria for the following reasons: The 5 new measurable lesions together represent at least 50 mm of the TMTB. Since PD is determined by at least a 20% increase in TMTB compared to the nadir, this means that the nadir TMTB for an organ needs to be 25 cm or two 10 cm lesions are required for irPD assessment, which is a significant tumor burden for any subject with cancer. This explains why measuring a total of 5 new lesions is sufficient and does not preclude the assessment of irPD. No more than 5 new lesions need to be measured. Larger lesions must be prioritized as new measurable lesions relative to smaller lesions in order to support the

irRC and WHO Criteria	Modification and Clarification of irRECIST	Rationale for Modification
		most conservative approach, as these larger lesions have a greater impact on the increase in TMTB% for irPD.
Non-index lesions at follow-up timepoints are contribute to the determination of irCR (Complete disappearance required)	**2.2 Follow-up: selection of non-target lesions** The definition of non-target lesion assessment in RECIST v1.1 evaluation criteria is used. Response of non-target lesions mainly contributes to the overall response assessment of irCR and irNon-CR/non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Even in the absence of TMTB progression, only severe and unequivocal worsening of non-target lesions alone may suggest irPD.	Non-target lesions have a dependent function. Such worsening should not be ignored in the event of large progression in non-target lesions and, in these rare cases, irPD based only on non-target lesions is a valid assessment option.
At follow-up timepoints, new non-measurable lesions are not allowed to be determined as and assessed as progression, which only prevent irCR.	**2.3 Follow-up: definition and assessment of new non-measurable lesions** All new lesions that are not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only large and unequivocal progression of new non-measurable lesions can lead to an overall assessment of irPD at this timepoint. Persistent new non-measurable disease may preclude irCR.	In these rare cases, irPD based only on new non-measurable lesions will be used as the assessment option when new non-measurable disease worsens severely.
irRC overall tumor assessment **irCR**, complete disappearance of all lesions (whether measurable or not and no new lesions) ≥ 50% reduction in tumor burden from baseline as confirmed by repeated serial	**2.4 irRC overall tumor assessment** **irCR**, complete disappearance of all measurable and non-measurable lesions. Lymph nodes must be reduced to < 10 mm in short axis. Confirmation of response is not required. irPR, ≥ 30% decrease from baseline in TMTB, non-target lesion is irNN, and no unequivocal progression of new non-measurable disease.	The irRECIST overall tumor assessment is based on the TMTB of measured target and new lesions, non-target lesion assessments, and new non-measurable lesions. The thresholds for irPR and irPD assessments are consistent with RECIST v1.1

irRC and WHO Criteria	Modification and Clarification of irRECIST	Rationale for Modification
assessments no less than 4 weeks from the date of first documentation of irPR. ● Confirmed irSD by continuous assessment at least 4 weeks after the first documentation, not meeting the criteria for irCR or irPR, and increased tumor burden by ≥ 25% in the absence of irPD. Relative to nadir (minimum tumor burden recorded) ● Confirmed by repeated serial assessments of no less than 4 weeks.	**irSD**, failing to meet the criteria for irCR or irPR in the absence of irPD. **irNN**, no target lesions are identified at baseline and follow-up, and the subject fails to meet the criteria for irCR or irPD. **irPD**, at least a 20% increase in TMTB compared to nadir and an absolute increase of at least 5 mm, or irPD in non-target or new non-measurable lesions. It is recommended that PD be confirmed at least 4 weeks after the first irPD assessment. **irNE** for special cases of insufficient data. **irND**, an aid in the absence of disease detection.	evaluation criteria and no response confirmation is required. Based on the expected efficacy of the compound, irPD-confirmed scans are recommended for subjects with at least a 20% increase in TMTB%, especially within the outbreak window of the first 12 weeks of treatment, to account for the expected delayed response.

Annex 5: American Cancer Federation (AJCC) 8th Edition nasopharyngeal carcinoma staging

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No tumor identified, but EBV-positive cervical node(s) involvement
T1	Tumor confined to nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumor with extension to parapharyngeal space, and/or adjacent soft tssue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension, involvement of Cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage
T4	Tumor with intracranial extension, involvement of Cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle

Defnition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC PROGNOSTIC STAGE GROUPS

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	Stage 0
T1	NO	M0	Stage I
T1,T0	N1	M0	Stage II
T2	N0	M0	Stage II

T2	N1	M0	Stage II
T1,T0	N2	M0	Stage III
T2	N2	M0	Stage III
T3	N0	M0	Stage III
T3	N1	M0	Stage III
T3	N2	M0	Stage III
T4	N0	M0	Stage IVA
T4	N1	M0	Stage IVA
T4	N2	M0	Stage IVA
Any T	N3	M0	Stage IVA
Any T	Any N	M1	Stage IVB

Annex 6: ECOG Performance Status Grading Scale

ECOG Grading Scale (Corresponding to Karnofsky Scale)

ECOG score	Karnofsky Score	Patient Status
0 point	90-100 points	Fully active, able to carry on all pre-disease performance without restriction.
1 point	70-80 points	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 points	50-60 points	Ambulatory and capable of all selfcare but unable to carry out any work activities. Ambulatory for ≥ 50% of waking hours.
3 points	30-40 points	Capable of only limited selfcare; confined to bed or chair > 50% of waking hours.
4 points	10-20 points	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5 points	0 point	Death.

Annex 7: Creatinine Clearance Calculation

Calculation of creatinine clearance by Cockcroft-Gault formula

Please select the formula correctly according to the different units used in serum creatinine test:

If serum creatinine concentration is calculated in mg/dL

$$\text{Creatinine Clearance for Men（mL/min）} = \frac{(140 - \text{Age}) \times (\text{Weight})}{72 \times \text{Serum creatinine}}$$

$$\text{Creatinine Clearance for Women（mL/min）} = \frac{0.85 \times (140 - \text{Age}) \times (\text{Weight})}{72 \times \text{Serum creatinine}}$$

If serum creatinine concentration is calculated in μmol/L

$$\text{Creatinine Clearance for Men（mL/min）} = \frac{(140 - \text{Age}) \times (\text{Weight})}{0.81 \times \text{Serum creatinine}}$$

$$\text{Creatinine Clearance for Women（mL/min）} = \frac{0.85 \times (140 - \text{Age}) \times (\text{Weight})}{0.81 \times \text{Serum creatinine}}$$

Note: The age is expressed in year, and weight in kg.

Annex 8: Contraceptive Measures, Definition of Women of Childbearing Potential, and Contraceptive Requirements

1. Background

Pregnancy: The safety and efficacy of this product in pregnant women have not been established.

Lactation: The safety and efficacy of this product in lactating women have not been established.

2. Definition of Women of Childbearing Potential

Women aged > 54 years whose menstruation ceased ≥ 12 months ago or who have undergone hysterectomy or bilateral oophorectomy or have been medically confirmed as ovarian failure are considered as women of non-childbearing.

Women aged ≤ 54 years (including those with any duration of amenorrhea) who have not undergone hysterectomy and bilateral oophorectomy and with no medically confirmed ovarian failure are considered as women of childbearing potential.

3. Contraceptive Requirements

Female subjects of childbearing potential must have a negative serum pregnancy test at screening prior to enrollment.

Subjects must also agree to one of the following procedures throughout the study:

- Total abstinence from sexual activities. Regular abstinence is not allowed (e.g., calendar method, ovulation period method, symptom-body temperature method, and post-ovulation method).
- Or correct use of condoms by male partners.
- Or correctly use one of the contraceptive methods listed below:
  - —Intrauterine device (IUD) with an annual failure rate < 1%
  - —Female barrier: cervical cap or dutch cap with spermicide
  - — Tubal sterilization
  - —Vasectomy for male partners

In addition to the above contraceptive measures, the subjects may also take the following contraceptive measures within 6 months after the study:

- —Hormone-containing contraceptives
- —Levonorgestrel implant
- —Injection of progesterone
- —Oral contraceptives (use of progesterone in combination or alone)
- —Vaginal contraceptive ring
- —Transdermal contraceptive patch

4. Male subjects shall agree to refrain from female sperm donation within 6 months after the end of study.

5. Procedures to be followed in the case of pregnancy.

If the subjects (or their partner) are pregnant at any time during the study, or if the subjects are pregnant within 6 months after the end of study (male subjects' partners are pregnant within 6 months), then the subjects shall notify the investigator according to the instructions.

Annex 9: Reference Principles for the Determination of irAEs

- Medical judgment and rationality assessment of individual AEs will be performed based on the characteristics of the event, temporal relationship to drug use, consistency with immune-related inflammation, response to corticosteroid therapy, and presence of any other definite pathogens.
- In this study, irAE refers to immune-related adverse reactions caused by KL-A167 injection.
- Cases that respond to treatment with corticosteroids is a priority for the diagnosis of irAEs.
- Exclude “not related” AEs determined by the investigator.
- If unlikely related, the analysis should be performed in combination with each case.
- Those having clear causes, such as infectious pneumonia, biliary obstruction, etc. can be excluded.
- All endocrine diseases with clear diagnostic indicators should be included, regardless of the use of “corticosteroids” or “hormone replacement therapy, such as insulin”;
- Interstitial lung disease with definite diagnosis should be included, regardless of the use of hormones.
- All Grade 3 or higher AEs that respond to corticosteroid therapy will be considered as irAEs.