Randomized controlled study of QL1706 combined chemotherapy versus chemotherapy for immune-treated non-small cell lung cancer

Trial cases

Program version number	**V2.0**
Version date	**April 21,2025**
Lead researcher	**Professor Yuan Shuanghu**
Lead research unit	**West District, First Affiliated Hospital of China University of Science and Technology**

declaration of secrecy

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Programme signature page

I have read and understood this trial protocol (Version: v2.0; Version Date: April 21,2025), and hereby consent to conduct this trial in accordance with its provisions and related supporting documents. I will provide the protocol to my research team and engage in discussions to ensure their full comprehension. I acknowledge that the collaborating organization may request termination of the trial or cessation of participant enrollment at any time for specified reasons, and I may terminate the trial to protect participants' rights. I hereby commit to strictly complying with all applicable regulations and Good Clinical Practice (GCP) standards throughout the trial.

At the same time, as the principal investigator of this trial, I coordinated the overall process of the trial.

surname and personal sign _____

name： _____

date： _____

catalogue

scenario summary

research topic	Randomized controlled study of QL1706 combined chemotherapy versus chemotherapy for immune-treated non-small cell lung cancer
project number	QL1706-NSCLC-A001
version number	V2.0
Lead researcher	Professor Yuan Shuanghu
Sponsor	West District, First Affiliated Hospital of China University of Science and Technology
Cooperative units	Qilu Pharmaceutical Co., LTD
Nature of study	Prospective, multicenter, open-label, randomized, controlled study
Type of study	Clinical trial initiated by the investigator (IIT)
subject investigated	Immune-treated locally advanced or recurrent/metastatic non-small cell lung cancer
purpose of research	To explore the efficacy and safety of combined chemotherapy with QU1706 compared with chemotherapy for immunotherapy in locally advanced or recurrent/metastatic non-small cell lung cancer
Number of patients planned for enrollment	96 cases
research on drug	QL1706：5mg/kg，iv，d1； Gisicitabine: 1000mg/m2, iv, d1, d8; Doxorubicin: 60mg/m2, iv, d1; Three weeks is a cycle
research design	This prospective, multicenter, open-label randomized controlled study enrolled 96 patients with immune-treated locally advanced or recurrent/metastatic non-small cell lung cancer. Participants were randomly assigned in a 1:1 ratio to either the experimental group receiving the combination of QL1706 and docetaxel or gemcitabine, or the control group receiving docetaxel or gemcitabine alone.

Point of research	**Main destinations:** ➢ Progression-Free Survival (PFS) Secondary endpoints: ➢ Objective Response Rate (ORR) ➢ Disease Control Rate (DCR) ➢ Relief duration (DOR, Duration of Response) ➢ Overall Survival (OS) ➢ Safety evaluation (AE, Adverse Events).
Sample size determination	This prospective, open-label, randomized controlled trial was designed based on literature data. The control group received standard chemotherapy with a median progression-free survival (mPFS) of 3 months, while the experimental group receiving the Aeto combination therapy (antibody plus chemotherapy and radiotherapy) had a projected mPFS of 6 months. With a total study duration of 24 months (including enrollment and follow-up), the mid-term enrollment time (assuming uniform enrollment rate) was set at 12 months. Using a significance level of α=0.05 and beta=0.2, the calculated sample size was 38 patients per group. Considering a 20% dropout rate, each group required 48 additional participants, resulting in a total enrollment of 96 patients.
Entry criteria	**Patients must meet all of the following criteria to be enrolled:** 1. Voluntary participation in the study and signing of informed consent; 2. Age ≥ 18 years old, ≤75 years old; 3. Diagnosed as NSCLC by histology or cytology; 4. No EGFR sensitive mutation or ALK gene translocation; 5. Patients who previously received PD-1/PD-L1 inhibitors and platinum-containing double-drug chemotherapy as first-line treatment for

Entry criteria	advanced metastatic or relapsed NSCLC and developed disease progression during or after treatment; 6. At least one measurable lesion as the target lesion (RECIST v1.1 criteria); 7. ECOG score: 0-2 points; 8. The survival period is expected to be no less than 12 weeks; 9. Women of childbearing age must have a negative pregnancy test (serum or urine) within 28 days prior to enrollment and voluntarily use appropriate methods of contraception during the observation period and for 8 weeks after the last dose; for men, surgical sterilization or consent to use appropriate methods of contraception during the observation period and for 8 weeks after the last dose; 10. Laboratory findings during the screening period indicate normal organ function: a) Hematology (no blood transfusion or hematopoietic cell/granulocyte colony factor therapy within 14 days): Neutrophil count (NEU) ≥1.5×10^9/L (1,500/mm³); Platelet count (PLT) ≥100×10^9/L (100,000/mm³); Hemoglobin ≥90 g/L; b) Liver: Total bilirubin (TBil) ≤ULN; Alanine aminotransferase (AST) and Aspartate aminotransferase (ALT) ≤1.5×ULN; AST or ALT 1.5-3.5×ULN; Alkaline phosphatase (ALP) ≤2.5×ULN; c) Kidneys: Calculated creatinine clearance (CrCl) ≥30 mL/min; d) Coagulation: International Normalized Ratio (INR) ≤1.5, with Prothrombin Time (PT) or Activated Partial Thromboplastin Time (APTT) ≤1.5×ULN; j) INR ≤1.5 and APTT ≤1.5×ULN.
Entry criteria	11. Patients who the researchers think could benefit.

Exclusion criteria	**Patients will not be eligible if they meet any of the following criteria:** 1. There are EGFR sensitive mutations or ALK gene translocation changes. 2. Had previously received PD1/CTLA4 bispecific antibody therapy; 3. The adverse reactions caused by previous treatment have not recovered to CTCAE (version 5.0) level 1 or below (except for the toxicity of level 2 or less that is judged by the investigator to be long-term, cannot be restored and does not increase safety risk); 4. Symptomatic central nervous system metastases. Patients who have received treatment for brain metastases and are considered stable by the investigator may be considered for participation in this study; 5. Patients with poorly controlled tumor-related pain who require analgesic treatment must receive a stable dose of treatment prior to participation in the study; 6. Patients with clinical symptoms or unstable chest water or ascites or pericardial effusion after symptomatic treatment; 7. Known to be susceptible to epalopritovorirelium and its components, planned chemotherapy drugs and those with a history of severe allergic reactions; 8. Patients with or suspected of having active autoimmune diseases, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, etc., excluding: type 1 diabetes and hypothyroidism that can be controlled by stable dose replacement therapy, and skin diseases (such as psoriasis, vitiligo) that do not require systemic treatment; 9. History of interstitial lung disease or drug-induced interstitial lung disease or pneumonia;
Exclusion criteria	

Exclusion criteria	10. Patients who received systemic corticosteroid drugs (Prednisone> 10mg/day or equivalent dose) or other immunosuppressive drugs within 14 days prior to study medication; 11. History of immune deficiency, including other acquired or congenital immune deficiency diseases, or history of organ transplantation, or allogeneic hematopoietic stem cell transplantation or solid organ transplantation; live vaccine vaccination within 4 weeks prior to the first study medication; 12. Patients with severe cardiovascular and cerebrovascular diseases: a) Uncontrolled hypertension or pulmonary hypertension; b) Unstable angina or history of myocardial infarction, coronary artery bypass grafting (CABG), or stent implantation within 6 months prior to study medication; c) Chronic heart failure with cardiac function grade ≥2 (New York Heart Association NYHA classification); d) Left ventricular ejection fraction (LVEF) <50%; e) Severe arrhythmias requiring pharmacotherapy (excluding atrial fibrillation or paroxysmal supraventricular tachycardia). Examples include: males with QTcF>450 msec or females with QTcF>470 msec, complete left bundle branch block (LBBB), or third-degree block; f) Cerebrovascular accidents (CVA) or transient ischemic attacks (TIA) within 6 months prior to study medication. 13. Positive human immunodeficiency virus (HIV) antibody test results with active hepatitis B or C. Participants may enroll in this study under the following conditions: a) Positive hepatitis B core antibody (HBcAb) or hepatitis B surface antigen (HBsAg), but HBV DNA levels below the research center's lower limit (negative) or <500 IU/mL, with clinical treatment and symptoms that researchers determine exclude active infection; b) Positive hepatitis C antibody with HCV

Exclusion criteria	RNA levels below the research center's lower limit (negative). 14. Having had any active malignancy other than the study disease within the last 5 years, except for malignancies that are expected to be cured by treatment (including but not limited to well-treated thyroid carcinoma, cervical carcinoma in situ, basal or squamous cell skin cancer, or breast ductal carcinoma in situ treated with radical surgery); 15. Those with a history of psychotropic drug abuse and unable to quit or those with a history of mental disorder; 16. Pregnant or lactating women; 17. The study authors believe the patient was not fit for any of the other conditions in this study.
Termination standards	The subject must withdraw/stop treatment if one or more of the following occurs: **1. Patients who showed disease progression on medical imaging and were judged by the investigator to have no benefit from continued medication;** **2. The subject is still unable to tolerate the toxicity after dose adjustment;** **3. The subject withdraws informed consent and requests to withdraw;** **4. Pregnancy events occurred in subjects during the study;** **5. The investigator identifies other circumstances that necessitate withdrawal from the study.**
Criteria for removal/removal	1. Failure to complete at least one cycle of clinical trial study according to this protocol due to non-test drug factors, and inability to evaluate safety and effectiveness; 2. Serious breach of protocol.

	3. Patients were not correctly enrolled in the study for treatment with the drug.
Duration of study	This study is expected to last 36 months, including a 24-month participant enrollment period, a 9-month follow-up period, and a 3-month data consolidation and report preparation period. (Additionally, the study timeline is a projected period. Any changes in enrollment or follow-up timing during actual implementation do not constitute protocol violations, until the completion of participant enrollment and the final participant's follow-up).
statistical treatment	The Kaplan-Meier method was used to plot the progression-free survival (PFS) curve with 95% confidence interval. The overall survival (OS) curve was constructed using the same method to estimate mean progression-free survival (mPFS), mean overall survival (mOS), and their corresponding 95% confidence intervals. ORR and DCR were calculated along with their 95% confidence intervals. Safety analysis primarily employed descriptive statistics, including tabular descriptions of adverse events (AEs) in this trial, covering incidence rates, severity levels, causality relationships, contributing factors, implemented interventions, and clinical outcomes.

Research flow chart

time / project	Screening period*		experimental stage					follow-up period		
			Period X				Treatment completion/withdrawal			
	D-28~D-7 (±7 days)	D-6~D1 (±7 days)	Day 1 of Week 2 (C2D1±7)	Day 1 of cycle 3 (C3D1±7)	Day 1 of Week 4 (C4D1±7)	Day 1 of X weeks (CxD1±7)		Safety25	Efficacy26	Survival27
basic data										
Sign informed consent	×									
Demographic data1	×									
Medical history2	×									
Combined medication3	×									
Laboratory/auxiliary examinations										
Blood routine4		×	×	×	×	×	×			
Routine urine5		×	×	×	×	×	×			
Blood Biochemistry6		×	×	×	×	×	×			

time / project	Screening period*		experimental stage					follow-up period		
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	D-28~D-7 (±7 days)	D-6~D1 (±7 days)	Day 1 of Week 2 (C2D1±7)	Day 1 of cycle 3 (C3D1±7)	Day 1 of Week 4 (C4D1±7)	Day 1 of X weeks (CxD1±7)		Safety25	Efficacy26	Survival27
Coagulation7		×	×	×	×	×	×			
Thyroid function test8		×	×	×	×	×	×			
Pregnancy test9	×						×			
Virological tests10	×						×			
Electrocardiogram11	×						×			
Ultrasound12	×						×			
clinical assessment										
Life signs13		×					×			
Physical14		×					×			
ECOG score15		×	×	×	×	×	×			

project \ time	Screening period*		experimental stage					follow-up period		
			Period X				Treatment completion/withdrawal			
	D-28~D-7 (±7 days)	D-6~D1 (±7 days)	Day 1 of Week 2 (C2D1±7)	Day 1 of cycle 3 (C3D1±7)	Day 1 of Week 4 (C4D1±7)	Day 1 of X weeks (CxD1±7)		Safety25	Efficacy26	Survival27
NYHA classify	×						×			
Adverse event16	From the date of informed consent to 28 days after the last medication									
End point indicators of efficacy and related evaluation										
Imaging studies17	×		Check at the end of each two weeks, and the allowable time window is ±7 days				×			
Progress of disease18									×	
Death19										×
research on drug										
QL170620		5mg/kg，iv，d1								
Gisicabine21		1000mg/m2，iv，d1、d8								

project \ time	Screening period*		experimental stage					follow-up period		
			Period X				Treatment completion/withdrawal			
	D-28~D-7 (±7 days)	D-6~D1 (±7 days)	Day 1 of Week 2 (C2D1±7)	Day 1 of cycle 3 (C3D1±7)	Day 1 of Week 4 (C4D1±7)	Day 1 of X weeks (CxD1±7)		Safety25	Efficacy26	Survival27
Doxorubicin22		60mg/m2，iv，d1								
Other records										
Distribution of drugs23		×								
Pharmaceutical recovery23		×								
Follow-up treatment of tumor24										

pour：

1. Demographic data (abbreviated name, gender, ethnicity, marital status, date of birth, height, weight);
2. Medical history: This includes the patient's prior history and treatment of driver gene-negative non-small cell lung cancer (NSCLC), covering clinical/pathological diagnosis, timing of diagnosis, clinical/pathological staging, EGFR status, microsatellite status; surgical intervention, neoadjuvant therapy, adjuvant therapy, radiotherapy, immunotherapy; other tumor history (excluding driver gene-negative NSCLC), smoking/alcohol consumption history (current or former use), medication allergies (drug names, allergic reactions), as well as comorbid conditions/symptoms (names, duration, treatment received, prognosis).

3. Compliance Monitoring: Document all concomitant medications from the screening period through study completion. These records must include: drug name, dosage, route of administration, frequency, therapeutic purpose, and start/end dates. If a participant initiates new systemic anti-tumor therapy during safety monitoring, only adverse events related to the investigational medication should be recorded as concomitant treatments.
4. Complete blood count (CBC) results obtained within 7 days prior to the first medication administration. This includes: red blood cell count (RBC), hemoglobin (Hb), white blood cell count (WBC), platelet count (PLT), and white blood cell differential [lymphocyte count (LYM) and neutrophil count (ANC)]. CBC tests are performed on the 21st±7th day of each treatment cycle and once at the time of treatment completion/withdrawal (if not conducted within 7 days).
5. Routine urinalysis results within 7 days prior to the first medication administration. This includes: Urinary white blood cells (UWBC), urinary protein (UPRO), urinary red blood cells (URBC), and urinary glucose (UGLU). Testing is conducted once per treatment cycle and once upon treatment completion/exit (if not performed within 7 days).
6. Blood biochemical tests shall be based on the results obtained within 7 days prior to the first medication administration. These include: liver function [total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin (ALB), total protein (TP)] and renal function [urea (UREA), serum creatinine (Cr)]. Fasting blood glucose (FBG) and lipid profile (triglycerides, cholesterol) are also required. When necessary, additional cardiac enzyme spectrum tests may be performed, including but not limited to creatine kinase (CK), creatine kinase-microsomal (CK-MB), α-hydroxybutyrate dehydrogenase (HBDH), and troponin T (cTnT), as determined by the investigator based on the subject's condition. Testing is conducted once per treatment cycle and once upon treatment completion/withdrawal (if not performed within 7 days).
7. The coagulation function was examined within 7 days before the first medication, once per cycle during the treatment period, and once at the end of treatment withdrawal (if not done within 7 days);
8. Examination results within 7 days before the first medication of thyroid function acceptance, once per cycle during treatment, and once at the end/withdrawal of treatment (if not performed within 7 days);
9. Pregnancy tests, women of childbearing age will have a urine or serum pregnancy test within 28 days prior to the first dose and at the time of the study treatment termination visit. If the urine pregnancy test result cannot be confirmed as negative, a serum pregnancy test will be performed with the serum pregnancy results being used as the criterion;

10. Viral testing requires test results from this center within 28 days prior to initial treatment initiation. During the screening phase, hepatitis B serology panel (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb), along with HCV antibody and HIV antibody tests will be conducted. HBsAg-positive cases will undergo HBV DNA testing, while HCV antibody-positive patients will receive HCV RNA testing. Additional tests may be performed when necessary. For hepatitis B virus carriers, regular viral activity monitoring is recommended throughout the study period, with one final test required upon treatment completion (if not conducted within 7 days).
11. Electrocardiogram: 12 lead electrocardiogram was used to detect the results within 28 days before the first medication in the screening period, and one test was performed at the end/treatment withdrawal (if not performed within 7 days prior);
12. Cardiac color Doppler ultrasound: Screening results must be obtained within 28 days prior to the first medication administration, with one final examination conducted at treatment completion or withdrawal (if not performed within the preceding 7 days). The primary monitoring focus is on changes in LVEF levels. If LVEF decreases to below 50% with a baseline decline of ≥10%, or if participants experience symptoms such as chest pain or palpitations, investigators may conduct additional examinations based on clinical circumstances.
13. Life signs: including body temperature, blood pressure, respiratory rate and heart rate; screening period (examination results within 7 days before the first medication), when the investigator deems it necessary during the trial, additional examinations may be added as appropriate; 1 examination at the end of treatment/withdrawal (if not performed within 7 days prior);
14. Physical Examination: This includes the head and face, skin system, lymph nodes, eyes, ears, nose, and throat, mouth, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, nervous system, and mental status. Comprehensive physical examination results are recorded during the screening period (within 7 days prior to initial medication administration) and at study completion. Investigators may add additional examinations as needed during the trial period. One check-up is required upon treatment completion/withdrawal (if not conducted within the previous 7 days).
15. ECOG score, screening period (test results within 7 days prior to first medication), treatment period once per cycle, and treatment completion/withdrawal assessment;
16. Adverse Events: Monitoring will commence on the day participants sign the informed consent form and continue until at least 28 days after the final study medication administration. Detailed documentation shall be maintained of adverse events, concomitant medications/treatment, and scheduled examinations throughout this period. Follow-up will continue until the adverse event resolves, the

participant initiates new anti-tumor therapy, or the investigator determines that the condition has reached a stable state that is no longer considered relapsed. Adverse Event (AE) and laboratory test safety evaluations will be conducted according to the NCI CTCAE 5.0 version.

17. Imaging examinations: The screening period includes pulmonary imaging, with additional chest-abdominal, cranial, neck, and pelvic scans as clinically indicated. Contrast-enhanced CT, MRI, or PET-CT may be used. Baseline tumor assessment can be relaxed to within 28 days prior to initial dosing. CT/MRI results obtained before informed consent signing that meet criteria may be used for screening evaluation. Routine bone scans are generally unnecessary unless bone metastasis is suspected, with whole-body bone scans permitted using results from within 2 months prior to initial dosing. Investigators may add scan sites during baseline or subsequent tumor evaluations as clinically indicated (for areas without baseline screening findings, investigators may adjust based on clinical practice). During the trial period, imaging examinations should be conducted every 2 cycles±7 under identical conditions (including contrast agent use) as baseline findings (bone scans are performed when bone progression is suspected or CR confirmation is required). New lesions should be examined promptly if suspected. The imaging window for tumors is ±7 days, with additional imaging allowed if disease progression (e.g., symptom worsening) is suspected. Treatment period imaging timing is determined at initiation of study therapy, excluding drug suspension due to toxic reactions. Non-screening period imaging allows ±7 days; participants withdrawing early for non-progression reasons (e.g., adverse events, management issues) will undergo a treatment completion evaluation upon withdrawal.
18. Disease Progression: For participants who discontinued trial treatment for reasons other than imaging-confirmed disease progression, if no imaging evaluation was performed within 28 days prior to trial termination, an imaging evaluation must be conducted at the time of treatment cessation. Additionally, tumor response should continue to be monitored according to the protocol-specified follow-up schedule until documented disease progression or initiation of new cancer therapy is confirmed.
19. Death: During the first year after treatment, survival status and subsequent anti-tumor treatment were collected every 3 months (±7 days) through clinical or telephone follow-up. From the second year after treatment, follow-up was conducted every 6 months (±15 days) until death;
20. QL1706:5mg/kg, iv, d1, record the time and dose of each injection;
21. Gisicabine: 1000mg/m2, iv, d1, d8, record the time and dose of each injection;

22. Doxorubicin: 60mg/m2, iv, d1, record the time and dose of each drug;
23. Drug recovery/distribution: Except for the drug distribution in the first cycle and the drug recovery after the end of treatment, the drug will be collected and distributed at the end of each cycle, and corresponding records will be made;
24. Follow-up of subsequent cancer treatment: it is necessary to record whether the subject has received other cancer treatment from the time of withdrawal or end of treatment until the death of the patient; it is not necessary to record the combined use of other diseases;
25. Safety Follow-up: From the date of informed consent to at least 28 days after the final study medication administration, investigators may select clinical evaluation measures such as complete blood count, biochemical tests, electrocardiogram (ECG), echocardiography, physical examination, vital signs, or ECOG score based on individual patient conditions for non-scheduled examinations. Adverse drug-related events shall be followed up until they disappear, reach baseline levels ≤1 grade, achieve stabilization, or are reasonably explained (e.g., loss to follow-up, death).
26. Efficacy Follow-up: Participants who are not PD or did not die were required to undergo efficacy follow-up. Starting from the end of the last tumor imaging assessment during the study period, participants received tumor imaging evaluations at least once every 12 weeks (±7 days) until either PD, initiation of other anti-tumor medications, or death (whichever occurred first). Detailed records were maintained for each follow-up time and tumor imaging evaluation results.
27. Survival Follow-up: All non-deceased subjects who complete safety and efficacy follow-up (with subsequent completion as the benchmark) must undergo survival follow-up. Starting from the date of completing safety and efficacy follow-up (with subsequent completion as the benchmark), telephone inquiries or clinical visits shall be conducted at least once every 3 months (±7 days) during the first year, and every 6 months (±14 days) thereafter. These visits shall involve the subject, their family members, or a local physician to collect survival information (death date and cause of death). The follow-up will continue until the subject's death, loss to follow-up, or completion of OS data collection (whichever occurs first). Each survival follow-up session must be meticulously documented.
28. All the examination items and frequencies in the flow chart are recommended. When necessary, the investigator can increase or decrease the frequency and examination items according to the actual clinical diagnosis and treatment of the subject and the status of the subject;

29. The laboratory and ancillary examination results involved in this study can be examined by an external hospital, and the results of the external hospital examination should be provided to the research center. The investigator will judge whether the results can be used for efficacy evaluation.

1. background information

1.1 Epidemiology and treatment status of driving gene negative non-small cell lung cancer

Lung cancer is the leading cause of cancer-related deaths globally. According to the 2023 Global Cancer Statistics, there were approximately 2.47 million new cases and 1.76 million deaths from lung cancer annually, accounting for 18.4% of all cancer-related deaths [1], with driver gene-negative NSCLC constituting about 30%-40% of all NSCLC cases. In China, lung cancer ranks first in both incidence and mortality rates, with approximately 870,000 new cases and 760,000 deaths reported in 2022 [2]. Among Chinese NSCLC patients, EGFR mutation rates are about 50%, ALK fusions about 5%, other mutations (ROS1, RET, etc.) about 5%-10%, and driver gene-negative proportions about 30%-40% [3]. Traditional therapies for driver gene-negative advanced non-small cell lung cancer have shown limited clinical efficacy. In recent years, the emergence of immune checkpoint inhibitors (ICI) has significantly transformed the treatment landscape for advanced non-small cell lung cancer patients, markedly extending overall survival in late-stage tumor patients.

Programmed Cell Death Receptor 1 (PD-1) and programmed cell death ligand 1 (PD-L1), among other immunotherapy drugs, have been among the most significant research advancements in oncology in recent years [4]. In advanced non-small cell lung cancer (NSCLC) patients, with the publication of Keynote and Checkmate series studies, pembrolizumab and nivolumab monotherapy have surpassed chemotherapy as single-line treatment regimens for advanced NSCLC [5]. In China, first-line indications for advanced NSCLC have been successively approved for pembrolizumab, sintilimab, carfilizumab, tislelizumab, and toripalimab [6]. For advanced driver gene-negative NSCLC, immunotherapy, especially PD-1 and PD-L1 inhibitors, has significantly improved patient prognosis, with a 5-year overall survival rate reaching 20%, and even up to 40% in patients with high PD-L1 expression [7]. Therefore, immunotherapy has become one of the standard treatment regimens recommended by the guidelines of the National Comprehensive Cancer Network (NCCN) and the Chinese Society of Clinical Oncology (CSCO) for first-line treatment of driver gene-negative advanced NSCLC,

and has become a mainstream therapeutic option in clinical practice. Nevertheless, a significant proportion of patients still show no response to treatment or only respond for a limited period. The median progression-free survival (mPFS) summarized from some clinical trials ranges from 4 to 10 months [8]. Research data shows that among 208 patients who developed acquired resistance after ICI use, 55.3% showed oligoprogression and 44.7% showed systemic progression. Oligoprogression is the primary progression pattern following immune therapy resistance [9]. For subsequent treatment of previously immunotherapy-treated patients, the current standard regimen remains chemotherapy-based. However, the efficacy of these programs is generally large and the side effects are large, which can not meet the current clinical treatment needs [10].

1.2 Current status of immunotherapy after treatment in driving gene negative non-small cell lung cancer

At present, there is no clinical treatment for patients with driving gene-negative advanced NSCLC who develop resistance to first-line immunotherapy or combination of immunotherapy and chemotherapy. Second-line chemotherapy such as docetaxel is the standard treatment recommended by NCCN guidelines and CSCO guidelines. A 2018 retrospective study by Park et al. [11] in South Korea enrolled 73 patients with NSCLC experiencing progression after immunotherapy (including nivolumab, pembrolizumab, or dutasterib), with 13.7% as second-line patients and 86.3% as subsequent-line patients. The treatment group received platinum-containing double-agent chemotherapy or monotherapy, achieving an objective response rate (ORR) of 53.4%, with progression-free survival (mPFS) of 4.2 months and overall survival (mOS) of 8.1 months. At the 2022 World Conference on Lung Cancer (WCLC), Auclin et al. [12] presented a multicenter retrospective analysis of 143 patients with advanced NSCLC who developed progression after first-line immunotherapy combined with chemotherapy. These patients received second-line treatments including platinum-based double-agent re-challenge regimens, paclitaxel ± anti-angiogenic therapy, or other chemotherapeutic agents (such as gemcitabine, vinorelbine, or pemetrexed). The results showed a disease control rate (DCR) of 38% and mOS of 8.1 months for second-line treatment. Notably, patients with first-line treatment responses lasting over 6 months demonstrated more significant benefits from second-line therapy, achieving an

mOS of 12.7 months. Another retrospective study conducted by Liu et al. [13], presented at the 2022 World Congress of Lung Cancer (WCLC), enrolled 467 patients with advanced NSCLC who had previously received either concurrent or sequential treatment with PD-1/PD-L1 inhibitors and platinum-based double-drug chemotherapy. These patients subsequently underwent subsequent treatment with paclitaxel monotherapy or paclitaxel combined with chemotherapy. The results indicated a median overall survival (mOS) of 8.9 months for those receiving paclitaxel as a second-line treatment. Therefore, this study suggests that for patients experiencing resistance to first-line immunotherapy or combination chemotherapy, second-line chemotherapy can still provide some survival benefit, though the gains are limited. This highlights the need to explore new therapeutic approaches.

The question of whether continuing immunotherapy after progression in patients with secondary resistance to immunotherapy has been a widely discussed issue, and some studies have explored the efficacy of continued immunotherapy following secondary resistance. A retrospective study published in 2021 by Xu et al. [9] included 208 stage IV NSCLC patients who developed progression after immunotherapy that had stabilized their disease for at least three months (at least two cycles). These patients received various treatment regimens post-progression, including continued immunotherapy, localized therapy, anti-angiogenic therapy, and combinations thereof. The results showed that patients who continued immunotherapy had significantly longer median overall survival (mOS) compared to those who discontinued immunotherapy (26.3 vs. 18.5 months). The BTCRC-LUN15-029 study, presented at the 2021 American Society of Clinical Oncology (ASCO) meeting, enrolled 35 patients with PD-1/PD-L1 inhibitors showing progression-free survival (PFS>3 months). Following PD treatment, these patients received pembrolizumab combined with adjuvant chemotherapy (gemcitabine, docetaxel, pemetrexed). The primary endpoints were progression-free survival (mPFS) of 5.2 months (RECIST 1.1 criteria) and overall survival (mOS) of 26.8 months. Among the participants, 23.5% achieved partial response (PR), while 53% showed stable disease (SD). Compared with historical controls receiving monotherapy, the combination of pembrolizumab and adjuvant chemotherapy demonstrated prolonged progression-free survival in advanced non-small cell lung cancer (NSCLC) patients with immune checkpoint inhibitors-induced disease progression [14]. The LUNG-MAP S1800A study was a randomized Phase II trial targeting stage IV or relapsed/refractory non-small cell lung cancer (NSCLC)

patients who had previously received immunotherapy. Participants were enrolled after 84 days of platinum-containing dual-drug combination/sequnized PD-1/PD-L1 therapy, with progression. They were randomly assigned in a 1:1 ratio to either pembrolizumab plus ramusosinib or investigator-selected standard chemotherapy regimens (docetaxel plus ramusosinib, docetaxel, gemcitabine, pemetrexed [for non-squamous cell carcinoma]). The median overall survival (mOS) was 14.5 months in the pembrolizumab group versus 11.6 months in the ramusosinib group. Compared with standard treatment regimens, the combination of pembrolizumab plus ramusosinib significantly improved survival in patients with prior chemotherapy and immunotherapy [15]. These findings suggest that for patients with first-line immunotherapy resistance or combination chemotherapy resistance, second-line immunotherapy re-challenge may still offer limited survival benefits, necessitating exploration of new treatment strategies.

Currently, numerous novel approaches targeting immune resistance in non-small cell lung cancer (NSCLC) patients are undergoing clinical trials. These include combinations of various immune checkpoint inhibitors, antibody-drug conjugates (ADCs), tumor vaccines, histone deacetylase inhibitors (HDACi), autologous tumor-infiltrating lymphocyte (TIL) therapy, and microbiota transplantation therapy. The combination of PD-1/PD-L1 inhibitors with novel immune checkpoint modulators such as CTLA-4, T-cell immunoglobulins, TIGIT (T cell immunoglobulin and ITIM domain protein), lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin mucins-3 (TIM-3) may serve as a potential strategy to overcome immune resistance. The RECLAIM study [16], a prospective Phase II trial, enrolled 30 patients with PD-L1-low (1%-49%) or PD-L1-negative (<1%) advanced NSCLC who had previously received chemotherapy or anti-PD-1 therapy. These patients were treated with a combination of PD-1 inhibitors (nivolumab) + CTLA-4 inhibitors (ipilimumab) + radiotherapy. The results showed 33% objective response rate (ORR) in patients with radiologically evaluable disease, demonstrating that the combination of PD-1 inhibitors, CTLA-4 inhibitors, and radiotherapy exhibits potent antitumor activity in immunorefractory patients with PD-L1-low or PD-L1-negative tumors.

1.3 The mechanism of action of QL1706

The injection formulation of Iparomlimab-Tuvonralimab (Drug Designator: QL-1706) is a novel combination antibody developed by Qilu Pharmaceutical Co., Ltd. This innovative therapeutic combines two engineered monoclonal antibodies in a fixed 2:1 ratio: Iparomlimab (PD-1-targeting IgG4 antibody) and Tuvonralimab (CTLA-4-targeting IgG1 antibody). The dual-action mechanism blocks both PD-1 and CTLA-4 simultaneously. The anti-PD-1 component utilizes a conventional IgG4 framework, preventing adhesion-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cell-mediated cytotoxicity (CDC) effects that could eliminate activated CD4+ and CD8+ T cells. This design preserves T-cell viability while enhancing interferon-γ (IFNγ) production within tumor microenvironments, thereby boosting immune efficacy. The anti-CTLA-4 component targets CTLA-4, an immune checkpoint molecule that inhibits T-cell activation. When binding to CTLA-4 on regulatory T cells (Tregs), the IgG1-based Tuvonralimab triggers ADCC-mediated cytotoxicity, eliminating tumor-suppressing Tregs and ultimately improving antitumor outcomes. Furthermore, to enhance therapeutic efficacy and safety, the Fc region of tovoririzumab was meticulously engineered to reduce its binding affinity with FcRs. This modification shortened the drug's half-life to one week while maintaining therapeutic effectiveness, effectively mitigating potential adverse reactions caused by prolonged CTLA-4 suppression. The combination of these two monoclonal antibodies (QL1706) creates a potent synergistic effect. While effectively reversing T-cell activation suppression and preserving effector T cell activity, it simultaneously targets Treg cells to improve the tumor microenvironment. This mechanism establishes a positive feedback loop within the tumor immune circuitry.

Preclinical studies demonstrated that in PD-1-resistant mouse models, the combination of QL1706 and chemotherapy significantly reduced tumor volume ($p<0.001$) without increasing immunotoxicity [17]. Furthermore, in the Phase I study of QL1706 [18],20 patients with immune-resistant non-small cell lung cancer achieved partial response (PR) in 3 cases, yielding an objective response rate (ORR) of 15% (95% CI: 3.2%-37.9%). The incidence of grade 3-4 treatment-related adverse events (TRAEs) was 12% across all dose groups, significantly lower than the 33% observed in

traditional dual-immunotherapy regimens like O+Y [19]. No treatment-related deaths occurred during the study.

In summary, immunotherapies remain a cornerstone treatment for advanced non-small cell lung cancer (NSCLC). However, the emergence of drug resistance after immunotherapy has significantly impacted patient survival and prognosis. While initial studies have explored resistance mechanisms, more research is needed to clarify key contributing factors and develop effective prevention strategies. Preclinical and Phase I clinical trials of QL1706 have demonstrated promising preliminary efficacy and good tolerability in PD-1-resistant NSCLC. Building on these findings, this study proposes an exploratory trial comparing QL1706 combined chemotherapy with monotherapy in treating immune-treated drive-negative NSCLC patients.

2. Research objectives and endpoints

2.1 Research purpose

To evaluate the efficacy and safety of combined chemotherapy with QU1706 in treating immune-mediated, driver gene-negative, non-small cell lung cancer.

2.2 Primary study endpoints

Progression-free survival (PFS): time from initiation of treatment to first disease progression or death from any cause;

2.3 Secondary study endpoints

Objective response rate (ORR): refers to the proportion of patients whose tumor volume is reduced by 30% and can be maintained for more than 4 weeks, that is, the sum of complete response and partial response (CR+PR).

Disease control rate (DCR): refers to the number of patients with tumors that have shrunk or remained stable and have remained stable for a certain period of time after receiving treatment with QL1706 combined chemotherapy or chemotherapy regimen;

Response duration (DOR): The time from the first assessment of complete or partial tumor response to the first assessment of tumor progression or death.

Overall survival (OS): time from initiation of medication to death due to any cause;

Adverse Events (AE): Collect all adverse events that occurred in subjects from the date of signing an informed consent to 28 days after discontinuation of medication. This includes clinical symptoms and abnormal vital signs, as well as abnormalities in laboratory tests. The clinical manifestations, severity, timing, duration, management methods, and prognosis of these events are recorded, along with their correlation to the investigational drug.

3. experiment design

3.1 system design

This prospective, multicenter, open-label randomized controlled study enrolled 96 patients with immune-treated driver gene-negative locally advanced or recurrent/metastatic non-small cell lung cancer. The patients were randomly assigned in a 1:1 ratio to receive the experimental group QL1706 combined with docetaxel or gemcitabine regimen, and the control group received docetaxel or gemcitabine regimen.

3.2 Duration of the study

This study is expected to last 36 months, including a 24-month enrollment period.

- Date of enrollment/entry of the first patient into the study: March 2025;
- Last patient enrollment date: February 2027;
- Date of study completion: November 2027 (9 months after the last eligible patient was enrolled);
- Database lock date: December 2027;
- Report date: February 2028.

Note: If the actual duration of the study changes, it is not a protocol violation.

4. Trial population

4.1 Sample size

This prospective, open-label, randomized controlled trial was designed based on literature data. The control group received standard chemotherapy with a median progression-free survival (mPFS) of 3 months, while the experimental group receiving the Aito combination therapy (antibody plus chemotherapy and radiotherapy) was projected to achieve a mPFS of 6 months. The total study duration (enrollment + follow-up) was 24 months, with a mid-term enrollment period of 12 months (assuming uniform enrollment rate). Using a significance level of α=0.05 and beta=0.2, the calculated sample size was 38 patients per group. Considering a 20% dropout rate, each group required 48 additional patients, resulting in a total enrollment of 96 patients.

4.2 Selection criteria

Participants must meet all of the following criteria to be enrolled:

1. Voluntary participation in the study and signing an informed consent form;
2. Age ≥ 18 years old, ≤75 years old;
3. Diagnosed as NSCLC by histology or cytology;
4. No EGFR sensitive mutation or ALK gene translocation;
5. Patients who previously received PD-1/PD-L1 inhibitors in combination with or sequential platinum-containing double drug chemotherapy as first-line treatment for advanced metastatic or relapsed NSCLC and who developed disease progression during or after treatment;
6. At least one measurable lesion as the target lesion (RECIST v1.1 criteria);
7. ECOG score: 0-2 points;
8. The survival period is expected to be no less than 12 weeks;
9. Women of childbearing age must have a negative pregnancy test (serum or urine) within 28 days prior to enrollment and voluntarily use appropriate methods of contraception during the observation period and for 8 weeks after the last dose; for

men, surgical sterilization or consent to use appropriate methods of contraception during the observation period and for 8 weeks after the last dose;

10. Laboratory findings during the screening period indicate normal organ function: a) Hematology (no blood transfusion or hematopoietic cell/granulocyte colony factor therapy within 14 days): Neutrophil count (NEU) ≥1.5×10^9/L (1,500/mm³); Platelet count (PLT) ≥100×10^9/L (100,000/mm³); Hemoglobin ≥90 g/L; b) Liver: Total bilirubin (TBil) ≤ULN; Alanine aminotransferase (AST) and Aspartate aminotransferase (ALT) ≤1.5×ULN; AST or ALT 1.5-3.5×ULN; Alkaline phosphatase (ALP) ≤2.5×ULN; c) Kidney: Calculated creatinine clearance (CrCl) ≥30 mL/min; d) Coagulation: International Normalized Ratio (INR) ≤1.5, with Prothrombin Time (PT) or Activated Partial Thromboplastin Time (APTT) ≤1.5×ULN; j) International Normalized Ratio (INR) ≤1.5; Activated Partial Thromboplastin Time (APTT) ≤1.5×ULN;
11. Patients who the researchers think could benefit.

4.3 Exclusion criteria

Participants will not be eligible for inclusion if they meet any of the following criteria:

1. The presence of EGFR sensitive mutation or ALK gene translocation;
2. Had previously received PD1/CTLA4 bispecific antibody therapy;
3. The adverse reactions caused by previous treatment have not recovered to CTCAE (version 5.0) level 1 or below (except for the toxicity of level 2 or less that is judged by the investigator to be long-term, cannot be restored, and does not increase safety risk);
4. Symptomatic central nervous system metastases. Patients who have received treatment for brain metastases and are considered stable by the investigator may be considered for participation in this study;

5. Patients with poorly controlled tumor-related pain who require analgesic treatment must receive a stable dose of treatment prior to participation in the study;
6. Patients with clinical symptoms or unstable chest, abdominal or pericardial fluid after symptomatic treatment;
7. Known to be susceptible to epalopritovorirelium and its components, planned chemotherapy drugs and those with a history of severe allergic reactions;
8. Patients with or suspected of having active autoimmune diseases, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, etc., excluding: type 1 diabetes and hypothyroidism that can be controlled by stable dose replacement therapy, and skin diseases (such as psoriasis, vitiligo) that do not require systemic treatment;
9. History of interstitial lung disease or drug-induced interstitial lung disease or pneumonia;
10. Patients who received systemic corticosteroid drugs (Prednisone> 10mg/day or equivalent dose) or other immunosuppressive drugs within 14 days prior to study medication;
11. History of immune deficiency, including other acquired or congenital immune deficiency diseases, or history of organ transplantation, or allogeneic hematopoietic stem cell transplantation or solid organ transplantation; live vaccine vaccination within 4 weeks prior to the first study medication;
12. Patients with severe cardiovascular and cerebrovascular diseases: a) Uncontrolled hypertension or pulmonary hypertension; b) Unstable angina or history of myocardial infarction, coronary artery bypass grafting (CABG), or stent implantation within 6 months prior to study medication; c) Chronic heart failure with cardiac function grade ≥2 (New York Heart Association NYHA classification); d) Left ventricular ejection fraction (LVEF) <50%; e) Severe arrhythmias requiring pharmacotherapy (excluding atrial fibrillation or paroxysmal supraventricular tachycardia). Examples include: males with QTcF>450 msec or females with QTcF>470 msec, complete left bundle branch block (LBBB), or third-degree block; f) Cerebrovascular accidents (CVA) or transient ischemic attacks (TIA) occurring within 6 months prior to study medication.

13. Positive human immunodeficiency virus (HIV) antibody test results with active hepatitis B or C. Participants may enroll in this study under the following conditions: a) Positive hepatitis B core antibody (HBcAb) or hepatitis B surface antigen (HBsAg), but HBV DNA levels below the research center's lower limit (negative) or <500 IU/mL, with clinical treatment and symptoms that researchers determine exclude active infection; b) Positive hepatitis C antibody with HCV RNA levels below the research center's lower limit (negative).
14. Having had any active malignancy other than the study disease within 5 years, except for those that are expected to be cured by treatment (including but not limited to well-treated thyroid carcinoma, cervical carcinoma in situ, basal or squamous cell skin cancer, or breast ductal carcinoma in situ treated with radical surgery);
15. Those with a history of psychotropic drug abuse and unable to quit or those with a history of mental disorder;
16. Pregnant or lactating women;
17. The study authors believe that the patient was not fit for any of the other conditions in this study.

4.4 Termination criteria

The subject must discontinue/treat if one or more of the following occurs:

1) Patients who show disease progression on medical imaging examination and are judged by the investigator to have no benefit from continued medication;

2) The subject is still unable to tolerate the toxicity after dose adjustment;

3) The subject withdraws the informed consent and requests to quit;

4) Pregnancy events occurred during the study;

5) Other circumstances in which the investigator considers it necessary to withdraw from the study.

4.5 Removal/removal criteria

The subject is excluded if one or more of the following conditions occurs:

1) Failure to complete at least one cycle of clinical trial study according to this protocol due to non-trial drug factors, and safety and effectiveness evaluation

cannot be performed;

2) Serious breach of the plan.

3) Patients were not correctly enrolled in the study for drug treatment.

5. Data collection management and research steps

5.1 Data collection plan

This study is divided into four phases: screening, trial, treatment completion/exit, and follow-up. Prior to enrollment, patients must read and sign the current ethics committee (EC)-approved informed consent form. All study procedures must be conducted within the timeframes specified in the study schedule. The duration for safety data collection runs from the date of informed consent (ICF) until 28 days after the last medication administration. Adverse events will be assessed according to the NCI CTCAE 5.0 criteria. All adverse events will be recorded in the Case Report Form (CRF) from ICF signing until study completion. Each participant will undergo scheduled visits, with specific data being documented at different time points during these visits.

The laboratory and ancillary test results involved in this study can be examined by an external hospital, and the results of the external hospital examination should be provided to the research center. The investigator will decide whether to accept the test results or re-examine them.

All examinations/inspections are recommended, and specific examinations/inspections are subject to clinical practice.

5.2 Filling in and transfer of case report form

The case report form is completed by the investigator, and each selected case must complete the case report form. After the completed case report form is reviewed by the clinical monitor, the first copy is transferred to the data administrator for data entry and management.

5.3 Database locking

After the data is reviewed and confirmed that the database is correct, the principal investigator, sponsor, and statistical analyst will lock the data. The locked data file will not be modified.

5.4 Screening period visits

After signing the informed consent form, the subject enters the screening period.

Physical examinations, vital signs, and laboratory tests (including complete blood count, urinalysis, biochemical blood tests, coagulation function, etc.) must be conducted within 7 days prior to initiating study treatment. Blood HCG levels, tumor imaging studies (head plain scan with contrast-enhanced MRI, chest-abdominal contrast-enhanced CT or MRI), 12-lead ECG, and echocardiography must be performed within 28 days prior to treatment initiation. For laboratory test results, imaging findings (bone scans permitted for results from two months prior to informed consent), 12-lead ECG, and cardiac color Doppler ultrasound obtained within 7 days before signing the informed consent form: If these tests sufficiently support the investigator's assessment of the subject's eligibility for enrollment criteria during the screening period, they need not be repeated; otherwise, retesting is required during the screening phase.

- Demographic data collection: demographic data (abbreviated name, gender, ethnicity, marital status, date of birth, height, weight);
- Medical history inquiry: This includes the patient's prior history and treatment of non-small cell lung cancer (clinical/pathological diagnosis, timing of diagnosis, clinical/pathological staging, EGFR status, microsatellite status; surgical intervention, neoadjuvant therapy, adjuvant therapy, radiotherapy, immunotherapy; other tumor conditions besides small cell lung cancer; smoking/alcohol consumption history (current status and cessation), drug allergies (medication names, allergic reactions), pre-existing or comorbid conditions/symptoms (disease/symptom names, duration, treatment received, prognosis);
- ECOG grade；
- Life signs: including body temperature, blood pressure, respiratory rate and heart rate;
- Physical examination: including head and face, skin system, lymph nodes, eyes, ears, nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen,

reproductive and urinary system, musculoskeletal, nervous system and mental state;

- Blood routine: including white blood cells, red blood cells, hemoglobin, platelets, neutrophils, lymphocytes absolute count;
- Urinary routine: including protein, sugar, red blood cells and white blood cells in urine;
- Blood Biochemistry: Includes total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, AKP, γ-GT, LDH, total protein, albumin, urea or blood urea nitrogen, creatinine, uric acid, fasting blood glucose, triglycerides, and cholesterol. When necessary, add cardiac enzyme spectrum tests including but not limited to creatine kinase (CK), creatine kinase isoenzyme (CK-MB), α-hydroxybutyrate dehydrogenase (BHD), and troponin T (cTnT), as determined by the investigator based on the subject's condition.
- Coagulation: including clotting time, thrombin time, prothrombin time, partial activated prothrombin time, etc.;
- Thyroid function test: including total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH);
- Pregnancy test: Women of childbearing age will have a urine or serum pregnancy test within 28 days prior to the first dose and at the time of the study treatment termination visit. If the urine pregnancy test result cannot be confirmed as negative, a serum pregnancy test will be performed with the serum pregnancy results being used as the criterion;
- Viral detection: including hepatitis B five (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) test, HCV antibody and HIV antibody test. If HBsAg is positive, further HBV DNA test will be conducted; if HCV antibody is positive, further HCV RNA test will be conducted;
- Electrocardiogram: 12 lead electrocardiogram was used for detection;
- Echocardiography: mainly followed up the changes of LVEF, such as when LVEF decreased to <50% and decreased by more than 10% compared with the baseline, or when subjects had chest pain, palpitations and other symptoms;
- Tumor imaging evaluation: The screening phase includes non-small cell lung cancer examinations. Additional scans such as abdominal, cranial, neck, pelvic, and bone scans may be added based on clinical indications when necessary, using enhanced CT, PET-CT, or MRI modalities. Baseline tumor assessment can be relaxed to include CT/MRI results obtained within 28 days prior to initial administration and within 7 days before signing informed consent, provided they meet eligibility criteria for screening. Routine bone scans are generally unnecessary unless bone metastasis is suspected. Whole-body bone scans should be performed using results from within two months prior to the first medication administration.
- Concomitant medication: The record of combined medication should include drug name, dosage, route of administration, frequency of administration, purpose of administration

and start and end date from the day of signing the informed consent;

- Adverse events: monitoring begins on the day of signing the informed consent form;
- After completing all the above screening assessments, qualified candidates are assigned a subject number.

5.5 Trial period

The treatment period begins with the first dose to the subject. The initial study medication should be administered as close as possible to the completion of screening tests and confirmation of eligibility criteria. Each treatment cycle is 3 weeks.

The following examinations must be completed within the timeframe specified in the trial protocol (±7 days). In case of statutory holidays, these may be advanced accordingly, with the reason for exceeding the deadline recorded in the Case Report Form (CRF). For participants residing outside the study region, the required examinations may be conducted at their local hospital starting from the second cycle (preferably performed at the participating center). The results should be communicated to the investigator, who will determine whether further testing at the research facility is necessary.

According to the clinical condition of the subjects, the researchers can increase the examination items or improve the frequency of visits to ensure the safety of the subjects to the greatest extent.

- ECOG score, vital signs, blood routine, blood biochemical, urine routine, coagulation, thyroid function: once per cycle, the investigator may increase the frequency of examination according to the clinical condition of the subject when necessary;
- Tumor imaging examinations: The timing for tumor imaging examinations during the treatment period is determined after the initiation of study treatment, excluding any drug suspension due to toxic reactions during this period. The allowable time window for tumor imaging examinations is ±7 days, with specific assessment time points as follows:
  - ✓ This will be assessed at the end of every 2 cycles until the subject progresses, becomes intolerant to toxicity, or begins new cancer treatment;
  - ✓ At the end of treatment or at the time of subject withdrawal (if no tumor assessment has been performed within the previous 4 weeks).

Note: During the treatment phase, imaging examinations should be conducted under the same conditions as baseline evaluations. Chest lesions identified at baseline should be re-evaluated every two treatment cycles. Baseline examinations for head and abdominal areas should also be

performed. Any new lesions detected beyond these criteria during the baseline period or suspected new lesions in later stages require timely follow-up. Additional imaging may be arranged when disease progression is suspected (e.g., symptom worsening). Patients with pre-existing bone metastases should undergo bone scans at least every 8 cycles (approximately 6 months), while routine bone scans are generally unnecessary unless bone metastasis is suspected.

- Concomitant medication/treatment: Record concomitant medication/treatment information during the study at any time;
- Adverse events: observe and record adverse events during the study at any time;
- Medication recovery/distribution: Keep records of medication recovery and distribution.

5.6 End of trial treatment/withdrawal from study

Participants continue treatment until disease progression, toxicity intolerance, withdrawal of informed consent, or the investigator determines that discontinuation is necessary. When study treatment is discontinued or participants withdraw from the study, if the patient has not undergone testing within 7 days prior to study completion (excluding tumor imaging evaluations), the following tests should be performed:

- ECOG grade；
- vital sign；
- check-up；
- routine blood test；
- routine urine test；
- Blood biochemistry;
- thyroid function；
- pregnancy tests；
- 12 leads electrocardiogram;
- Cardiac color ultrasound;
- Tumor imaging: if not performed within the last 4 weeks;
- Combined medication/therapy: real-time recording;
- Adverse events: real-time recording;

5.7 Follow-up period

The follow-up period begins the day after the last medication of the subject is determined to be in the group and will continue until the completion of survival follow-up (those who did not receive medication at enrollment do not need to be followed up), or 9 months after the last subject is enrolled, or the study is considered to be terminated early by the investigator.

- Safety Follow-up: At least 28 days after the last study medication administration, investigators may select clinical evaluation measures such as complete blood count, biochemical tests, coagulation profiles, thyroid function tests, electrocardiograms, echocardiograms, physical examinations, vital signs, or ECOG scores based on the subject's specific condition. These will be recorded as scheduled follow-up evaluations. The follow-up must continue until all severe or drug-related toxicities have resolved to NCI-CTC-AE 5.0 Grade I or lower, the subject initiates new anti-tumor therapy, or the investigator determines that the condition has stabilized at an unrelieved level (whichever occurs first).
- Efficacy Follow-up: For participants withdrawn due to non-disease progression or non-fatal reasons, tumor imaging assessments shall be conducted every 12 weeks (±7 days) starting from the end of the last tumor imaging evaluation during the study period. These assessments will continue until either PD, initiation of other anti-tumor medications, or death (whichever occurs first). Detailed records shall be maintained for each follow-up time and tumor imaging evaluation results.
- Survival Follow-up (OS Data Collection): All non-murdered subjects who completed safety and efficacy follow-up (with subsequent completion as the benchmark) are required to undergo survival follow-up. Starting from the completion of these follow-up procedures (with subsequent completion as the benchmark), follow-ups will be conducted every 3 months (±7 days) during the first year after treatment termination. From the second year onward, follow-ups will be performed every 6 months (±14 days) via telephone interviews or clinical visits with the subjects, their family members, or local physicians to collect survival information (death date and cause of death). This process will continue until the subject's death, loss of contact, or completion of OS data collection (whichever occurs first). Each survival follow-up must be meticulously documented and entered into the corresponding CRF form.

The following table lists the follow-up and evaluation items, and all data from these evaluations must be recorded in the subject's original file.

project \ time	Screening period*		experimental stage					follow-up period		
			Period X				Treatment completion/withdrawal			
	D-28~D-7 (±7 days)	D-6~D1 (±7 days)	Day 1 of Week 2 (C2D1±7)	Day 1 of cycle 3 (C3D1±7)	Day 1 of Week 4 (C4D1±7)	Day 1 of X weeks (CxD1±7)		Safety25	Efficacy26	Survival27
basic data										
Sign informed consent	×									
Demographic data1	×									
History2	×									
Combined medication3	×									
Laboratory/auxiliary examinations										
Blood routine4		×	×	×	×	×	×			
Routine urine5		×	×	×	×	×	×			
Blood Biochemistry6		×	×	×	×	×	×			
Coagulation7		×	×	×	×	×	×			

project \ time	Screening period*		experimental stage					follow-up period		
			Period X				Treatment completion/withdrawal			
	D-28~D-7 (±7 days)	D-6~D1 (±7 days)	Day 1 of Week 2 (C2D1±7)	Day 1 of cycle 3 (C3D1±7)	Day 1 of Week 4 (C4D1±7)	Day 1 of X weeks (CxD1±7)		Safety25	Efficacy26	Survival27
Thyroid function test8		×	×	×	×	×	×			
Pregnancy test9	×						×			
Virological tests10	×						×			
Electrocardiogram11	×						×			
Ultrasound/心动图12	×						×			
clinical assessment										
Life signs13		×					×			
Physical14		×					×			
ECOG score15		×	×	×	×	×	×			
NYHA classify	×						×			

project \ time	Screening period*		experimental stage					follow-up period		
	D-28~D-7 (±7 days)	D-6~D1 (±7 days)	Period X				Treatment completion/withdrawal	Safety25	Efficacy26	Survival27
			Day 1 of Week 2 (C2D1±7)	Day 1 of cycle 3 (C3D1±7)	Day 1 of Week 4 (C4D1±7)	Day 1 of X weeks (CxD1±7)				
Adverse event16	From the date of informed consent to 28 days after the last medication									
End point indicators of efficacy and related evaluation										
Imaging studies17	×		Check at the end of each two weeks, and the allowable time window is ±7 days				×			
Progress of disease18									×	
Death19										×
research on drug										
QL170620		5mg/kg，iv，d1								
Gisicabine21		1000mg/m2，iv，d1、d8								
Doxorubicin22		60mg/m2，iv，d1								

project \ time	Screening period*		experimental stage					follow-up period		
			Period X				Treatment completion/withdrawal			
	D-28~D-7 (±7 days)	D-6~D1 (±7 days)	Day 1 of Week 2 (C2D1±7)	Day 1 of cycle 3 (C3D1±7)	Day 1 of Week 4 (C4D1±7)	Day 1 of X weeks (CxD1±7)		Safety25	Efficacy26	Survival27
Other records										
Distribution of drugs23		×								
Pharmaceutical recovery23		×								
Follow-up treatment of tumor24										

pour：

1. Demographic data (abbreviated name, gender, ethnicity, marital status, date of birth, height, weight);
2. Medical history: This includes the patient's prior history and treatment of driver gene-negative non-small cell lung cancer (NSCLC), covering clinical/pathological diagnosis, timing of diagnosis, clinical/pathological staging, EGFR status, microsatellite status; surgical intervention, neoadjuvant therapy, adjuvant therapy, radiotherapy, immunotherapy; other tumor-related medical history (excluding driver gene-negative NSCLC), smoking/alcohol consumption history (current or former use), drug allergy history (medication names, allergic reactions), as well as comorbid conditions/symptoms (disease/symptom names, duration, treatment received, and outcomes).
3. Compliance Monitoring: Document all concomitant medications from the screening period through study completion. The documentation should include drug names, dosages, administration routes, frequencies, therapeutic purposes, and dates of start and end. If a participant

initiates new systemic anti-tumor therapy during safety monitoring, only records adverse events related to the study medication's concomitant treatments shall be included.

4. Complete blood count (CBC) results obtained within 7 days prior to the first medication administration. This includes: red blood cell count (RBC), hemoglobin (Hb), white blood cell count (WBC), platelet count (PLT), and differential leukocyte count [lymphocyte count (LYM), neutrophil count (ANC)]. CBC tests are performed on the 21st±7th day of each treatment cycle, with one additional test required upon treatment completion or discontinuation (if not conducted within 7 days).
5. Routine urinalysis results within 7 days prior to the first medication administration. This includes: Urinary white blood cells (UWBC), urinary protein (UPRO), urinary red blood cells (URBC), and urinary glucose (UGLU). Testing is conducted once per treatment cycle and once upon treatment completion/withdrawal (if not performed within 7 days).
6. Blood biochemical tests shall be based on the results obtained within 7 days prior to the first medication administration. These include: liver function [total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin (ALB), total protein (TP)] and renal function [urea (UREA), serum creatinine (Cr)]. Fasting blood glucose (FBG) and lipid profile (triglycerides, cholesterol) are also required. When necessary, additional cardiac enzyme spectrum tests may be performed, including but not limited to creatine kinase (CK), creatine kinase-microsomal (CK-MB), α-hydroxybutyrate dehydrogenase (HBDH), and troponin T (cTnT), as determined by the investigator based on the subject's condition. Testing is conducted once per treatment cycle and once upon treatment completion/exit (if not performed within 7 days).
7. The coagulation function was examined within 7 days before the first medication, once per cycle during the treatment period, and once at the end of treatment withdrawal (if not done within 7 days);
8. Examination results within 7 days before the first medication of thyroid function acceptance, once per cycle during the treatment period, and once at the end/withdrawal of treatment (if not performed within 7 days);
9. Pregnancy tests, women of childbearing age will have a urine or serum pregnancy test within 28 days prior to the first dose and at the time of the study treatment termination visit. If the urine pregnancy test result cannot be confirmed as negative, a serum pregnancy test will be performed and the serum pregnancy result will prevail;
10. Viral testing requires test results from this center within 28 days prior to initial treatment initiation. During the screening phase, hepatitis B serology panel (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb), along with HCV antibody and HIV antibody tests will be conducted. HBsAg-

positive cases will undergo HBV DNA testing, while HCV antibody-positive patients will receive HCV RNA testing. Additional tests may be administered when necessary. For hepatitis B virus carriers, regular viral activity monitoring is recommended throughout the study period, with one final test required upon treatment completion/withdrawal (if not performed within 7 days).

11. Electrocardiogram: 12 lead electrocardiogram was used to detect the results within 28 days before the first medication in the screening period, and one test was performed at the end/treatment withdrawal (if not performed within 7 days prior);
12. Cardiac color Doppler ultrasound: Screening results must be obtained within 28 days prior to the first medication administration, with one final examination conducted at treatment completion/withdrawal (if not performed within the preceding 7 days). The primary monitoring focus is on changes in LVEF levels. If LVEF decreases to below 50% with a baseline decline of ≥10%, or if participants experience symptoms such as chest pain or palpitations, investigators may conduct additional examinations based on clinical circumstances.
13. Life signs: including body temperature, blood pressure, respiratory rate and heart rate; screening period (examination results within 7 days before the first medication), when the investigator deems it necessary during the trial, additional examinations may be added as appropriate; one examination at the end of treatment/withdrawal (if not performed within 7 days prior);
14. Physical Examination: This includes the head and face, skin system, lymph nodes, eyes, ears, nose, and throat, mouth, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, nervous system, and mental status. Comprehensive physical examination results are recorded during the screening period (within 7 days prior to initial medication administration) and at study completion. Investigators may add additional examinations as needed during the trial period. One check-up is required upon treatment completion/withdrawal (if not conducted within the previous 7 days).
15. ECOG score, screening period (test results within 7 days prior to first medication), treatment period once per cycle, and treatment completion/withdrawal assessment;
16. Adverse Events: Monitoring will commence on the day participants sign the informed consent form and continue until at least 28 days after the final study medication administration. Detailed documentation will include adverse events, concomitant medications/therapies, and scheduled unannounced examinations throughout this period. Follow-up will continue until the adverse event resolves, the participant initiates new anti-tumor therapy, or the investigator determines that the condition has reached a stable, non-resolvable state. Adverse Event (AE) and laboratory test safety evaluations will be conducted according to the NCI CTCAE 5.0 version.

17. Imaging examinations: The screening period includes pulmonary imaging, with additional chest-abdominal, cranial, neck, and pelvic examinations as clinically indicated. Contrast-enhanced CT, MRI, or PET-CT may be used. Baseline tumor assessment can be relaxed to within 28 days prior to initial dosing, provided CT/MRI results obtained before informed consent meet eligibility criteria for screening evaluation. Routine bone scans are generally unnecessary unless bone metastasis is suspected, with whole-body bone scans permitted using results from within two months prior to initial administration. Investigators may add scan sites during baseline or subsequent tumor evaluations as clinically indicated (for non-metastatic areas identified during screening, investigators may adjust based on clinical practice). During the trial period, imaging examinations should be conducted every 2 cycles±7 under identical conditions to baseline scans (including contrast agent use), with bone scans performed when bone progression is suspected or for CR confirmation. New lesions should be examined promptly if identified. The allowable time window for tumor imaging is ±7 days, with additional imaging permitted if disease progression is suspected (e.g., symptom worsening). Treatment duration-based imaging timing starts from the initiation of study therapy, excluding periods when dosing is paused due to toxic reactions. For non-commissioned participants, the allowable time window for post-screening imaging is ±7 days. If participants withdraw early due to non-disease progression reasons (e.g., adverse events, management issues), a final treatment completion evaluation should be conducted upon withdrawal.
18. Progression of Disease: For participants who discontinued trial treatment for reasons other than imaging-confirmed disease progression, if no imaging evaluation was performed within 28 days prior to trial termination, an imaging evaluation must be conducted at the time of treatment termination. Additionally, tumor response should continue to be monitored at the prescribed follow-up frequency specified in the protocol until documented disease progression or initiation of new cancer therapy.
19. Death: During the first year after treatment, survival status and subsequent anti-tumor treatment were collected every 3 months (±7 days) through clinical or telephone follow-up. From the second year after treatment, follow-up was conducted every 6 months (±15 days) until death;
20. QL1706:5mg/kg, iv, d1, record the time and dose of each injection;
21. Gisicabine: 1000mg/m2, iv, d1, d8, record the time and dose of each injection;
22. Doxorubicin: 60mg/m2, iv, d1, record the time and dose of each drug;

23. Drug recovery/distribution: Except for the drug distribution in the first cycle and the drug recovery after the end of treatment, the drug will be collected and distributed at the end of each cycle, and corresponding records will be made;
24. Follow-up of subsequent cancer treatment: it is necessary to record whether the subject has received other cancer treatment from the time of withdrawal or end of treatment until the death of the patient; it is not necessary to record the combined use of other diseases;
25. Safety Follow-up: From the date of informed consent to at least 28 days after the final study medication administration, investigators may select clinical evaluation measures such as complete blood count, biochemical tests, electrocardiogram (ECG), echocardiography, physical examination, vital signs, or ECOG score as scheduled follow-up records based on individual patient conditions. Adverse drug-related events shall be followed up until they disappear, reach baseline levels ≤1 grade, achieve stabilization, or are reasonably explained (e.g., loss to follow-up, death).
26. Efficacy Follow-up: Participants who are not PD or did not die were required to undergo efficacy follow-up. Starting from the end of the last tumor imaging assessment during the study period, participants received tumor imaging evaluations at least once every 12 weeks (±7 days) until either PD, initiation of other anti-tumor medications, or death (whichever occurred first). Detailed records were maintained for each follow-up time and tumor imaging evaluation results.
27. Survival Follow-up: All non-murdered subjects who complete safety and efficacy follow-up (with subsequent completion as the benchmark) must undergo survival follow-up. Starting from the date of completing these follow-up procedures (with subsequent completion as the benchmark), telephone inquiries or clinical visits shall be conducted at least once every 3 months (±7 days) during the first year, and every 6 months (±14 days) thereafter. These visits shall involve the subject, their family members, or a local physician to collect survival information (death date and cause of death). The follow-up will continue until the subject's death, loss to follow-up, or completion of OS data collection (whichever occurs first). Detailed records shall be maintained for each survival follow-up session.
28. All the examination items and frequencies in the flow chart are recommended. When necessary, the investigator can increase or decrease the frequency and examination items according to the actual clinical diagnosis and treatment of the subject and the status of the subject;
29. The laboratory and ancillary examination results involved in this study can be examined by an external hospital, and the results of the external hospital examination should be provided to the research center. The investigator will judge whether the results can be used for efficacy evaluation.

6. Trial drug

6.1 Drug Name and Specifications

0. QL1706:50mg (2ml)/bottle. Developed by Qilu Pharmaceutical Co., LTD. Store at 2-8 degrees Celsius, light and sealed.
1. Gisicabine: 0.2g per vial. Developed by Qilu Pharmaceutical Co., Ltd. Store at room temperature (15℃ to 30℃) in a sealed container.
2. Doxorubicin: 20mg (1ml)/piece, developed by Qilu Pharmaceutical Co., LTD. 2-8 degrees, lightproof, sealed storage.

6.2 Drug management

3. QL1706 Injection The investigational drug was administered on the first day of each visit and administered in accordance with the requirements and specifications at the hospital.
4. Gisicitabine The investigational drug was administered on the first day of each visit and injected at the hospital as required and in accordance with specifications.
5. Doxorubicin The investigational drug was administered on the first day of each visit and administered in accordance with the required specifications at the hospital.
6. The test center shall keep all the test drugs in a safe and compliant place, and be managed by a special person (drug receiving, storage, distribution, recovery, etc.).
7. Researchers in charge of drug management need to record the number of drugs distributed and returned per subject at each follow-up visit, as well as the corresponding date of follow-up.
8. All investigational drugs entering or leaving the clinical trial facility shall be

documented (including unused drugs and packaging). Participants must return all unused drugs and empty packaging to the investigator during each follow-up visit. At the end of the trial, the investigator will return them to the sponsor for inventory and destruction.

6.4 Combination therapy

During the trial, the subjects may receive appropriate supportive treatment for adverse events in addition to the trial drug. Other anti-tumor treatments shall not be taken during the study to avoid affecting the evaluation of the efficacy of the trial drug. The specific regulations are as follows:

- Throughout the study, subjects were not allowed to use any systemic anti-tumor measures other than the investigational drug, which could be combined with local treatment.
- After evaluating the relationship between adverse events and trial medications, researchers may implement appropriate supportive therapies. These treatments, including antiemetics, antidiarrheals, antipyretics, antihistamines, anti-rash medications, antihypertensive drugs, analgesics, antibiotics, and other interventions such as blood products, should be documented in the Case Report Form (CRF) with their start and duration.
- Non-hematological toxicity can be treated with appropriate medication at grade 2 and recorded in the combined medication.
- Blood toxicity can be treated with appropriate medication at level 3 and recorded in the combined medication.
- When the subject's hemoglobin is 5.0g/L-8.0g/L, it is up to the investigator to decide whether erythropoietin (EPO) therapy should be given; when hemoglobin is <5.0g/L, component transfusion should be given.
- When the subject's platelet count was <50.0×109/L, interleukin-11 or thrombopoietin (TPO) was administered; if the platelet count was <25.0×109/L or bleeding tendency occurred, component transfusion was administered.

- When the neutrophil count of the subject is <1.0~0.5 × 109 /L but without fever, the investigator decides whether to give cytokine therapy such as G-CSF; if grade 3 neutropenia with temperature above 38.5℃ or grade 4 neutropenia occurs, cytokine therapy should be given.
- For subjects who were already using bone regulators (e.g., bisphosphonates, RANK ligands, etc.) prior to the screening period, the original drug and dose should be maintained during the trial; for subjects who did not use bone regulators prior to the screening period, it is not recommended to add bone regulators during the trial.
- All information about concomitant drugs received by the subject (generic name of the drug, purpose of administration, dosage, time of administration, etc.) should be fully recorded in the original data.

7. Efficacy evaluation

7.1 Efficacy evaluation criteria

- The efficacy was evaluated according to the RECIST v1.1 version (2009) criteria for solid tumors (see appendix). The efficacy was divided into four grades: complete response, partial response, disease progression and stability.
- Complete remission (CR): All lesions are gone. The short diameter of all pathological lymph nodes (including target and non-target nodes) must be reduced to <10mm, and tumor markers return to normal levels.
- Partial response (PR): The total length of the target lesion LD decreased by at least 30% compared with the total length of the baseline lesion LD.
- Progression (PD): The total number of lesions with LD at the target site is increased by at least 20% compared to the minimum number of lesions with LD recorded since the start of treatment, and the absolute number of lesions with LD is increased by at least 5mm. Progression is also considered when one or more new lesions are present.
- Stable disease (SD): the degree of reduction of the target lesion is not up to PR, and the degree of increase is not up to PD level, between the two. During

the study, the minimum value of the sum of diameters can be used as a reference.

7.2 Efficacy evaluation methods

The size of the subject's lesion is assessed by imaging (including CT, MRI, bone scan, or other imaging data that the investigator considers to be of therapeutic value). The imaging method used for all follow-up times in the subject must be consistent with the baseline.

7.3 Intervals for Efficacy Evaluation

During the study treatment, an assessment was performed every 2 treatment cycles (±7 days) until disease progression or initiation of new anti-tumor therapy (whichever occurred first).

If a subject withdraws from the study for reasons other than disease progression (such as adverse events, management reasons, etc.), an end-of-treatment assessment will be performed at the time of withdrawal.

8 Detection of adverse events

8.1 Adverse events

Adverse Event (AE) is defined as any adverse medical event that occurs in a subject following administration of the investigational drug. These events may manifest as symptoms, signs, disease manifestations, or abnormal laboratory findings, though not necessarily causally related to the investigational drug. This includes recurrence of pre-existing conditions during clinical trials, regardless of whether treatment-related. Clinical invasive procedures themselves are not considered adverse events, but the underlying causes of these procedures should be classified as adverse events.

Events occurring at the pre-and post-treatment stages are also considered AE according to regulations. Therefore, safety monitoring of AE or SAE reporting should

begin when the subject enters the study (signs an informed consent) and end at the study completion visit.

8.2 Classification of adverse events

Refer to the NCI-CTCAE 5.0 version for the classification of adverse drug events. If an adverse event is not listed in the NCI-CTCAE 5.0 version, refer to the following criteria:

grade	Clinical description of severity
1	Mild; no clinical symptoms or with mild clinical symptoms; only clinical or laboratory abnormalities; no treatment required
2	Moderate; requires small, local or non-invasive treatment; age-appropriate limitations in the use of tools for daily living activities (ADLs), use of tools for daily living refers to cooking, shopping, phone calls, counting money, etc
3	The condition is severe or presents with serious medical symptoms that are not immediately life-threatening; requires hospitalization or prolonged hospital stays; leads to disability; or impairs the ability to perform self-care activities (ADLs). Self-care activities include: bathing, dressing and undressing, eating, using the bathroom, taking medication, etc. This does not mean being bedridden.
4	Life-threatening; requires urgent treatment
5	Causes death

8.3 Judgment of the relationship between adverse events and treatment

The potential association between adverse events (AEs) and treatment modalities was evaluated using a five-level classification system (definite, probable, possible, possible, and none) (see Table 1). The first three levels indicate treatment-related associations. When calculating the incidence of adverse reactions, the three categories are combined as the numerator, with the total number of participants evaluated for safety as the denominator.

Table 1 Criteria for AE and treatment

standard	Must be related	Probably related	Probably relevant	It may not matter	have nothing to

					do with
Reasonable chronological order	yes	yes	yes	yes	deny
Known types of drug reactions	yes	yes	yes	deny	deny
The cause can be improved by removal	yes	yes	Yes or no	Yes or no	deny
Re-dosing can repeat	yes	?	?	?	deny
There may be another explanation for the reaction	deny	deny	deny	yes	yes

8.4 Serious Adverse Events (SAE)

(1) Definition of serious adverse events

Serious adverse events (SAE) refer to medical events that occur during clinical study and require hospitalization or prolonged hospital stay, disability, impairment of work capacity, life-threatening or fatal, or leading to congenital malformations. They include the following medical events:

- -Mortal incidents;
- Life-threatening events (defined as a risk of immediate death to the subject at the time of the event);
- Events requiring hospitalization or prolonged hospital stay;
- Events that may lead to permanent or severe disability/function impairment/impact on work capacity;
- Congenital abnormalities or birth defects; `
- Other significant medical events (defined as events that endanger the subject or require intervention to prevent the occurrence of any of these conditions).

(2) encyesis

If a subject becomes pregnant during the clinical trial, the subject is withdrawn from the group. The investigator shall report to the sponsor within 24 hours of learning of the pregnancy and report to the ethics in a timely manner.

(3) Disease progression and death

Disease progression is defined as a subject's condition worsening caused by the trial medication's intended indication, including imaging findings and clinical symptom or sign progression. The emergence of new metastatic lesions relative to the primary tumor or progression of existing metastases is considered disease progression. Life-threatening events requiring hospitalization or prolonged hospital stays, or those resulting in permanent disability/function impairment/work capacity loss, congenital abnormalities, or birth defects caused by symptoms/signs of disease progression are not accelerated reporting as SAEs. Deaths caused by symptoms/signs of disease progression are reported as accelerated SAEs. If there is any uncertainty regarding whether an SAE was caused by disease progression, it should be reported as an SAE.

In this study population, disease progression is an expected occurrence. The term "disease progression" should not be reported as an adverse event (AE). When a participant experiences a confirmed progression event, it must be documented as an AE. For example, if a participant develops epilepsy that is determined to be associated with brain metastasis, the AE should be recorded as "epilepsy" rather than "disease progression" or "brain metastasis".

The term "death" should not be used as an AE or SAE term, but as the outcome of the event. Events that cause or lead to death should be recorded as AE or SAE. If the cause of death is unknown and cannot be determined at the time of reporting, the AE or SAE term should be recorded as "cause of death unknown".

(4) Other antitumor treatments are being administered

If a participant initiates other anti-tumor therapy within 30 days after the last use of the study drug, only those serious adverse events related to the study drug will be collected following the start of new anti-tumor treatment. If death occurs within 30 days after the last use of the study drug, it must be promptly reported as a serious adverse event regardless of whether the participant is receiving other treatments.

(5) hospitalization

Adverse events in clinical studies that lead to hospitalization or prolonged length of stay should be considered serious adverse events. Any initial admission to a medical institution (even less than 24 hours) meets this criterion.

Hospitalization does not include the following:

- rehabilitation agency
- sanatorium

- Admission to the general emergency room
- Same-day surgery (e.g. outpatient/day/non-bed surgery)

Hospitalization or prolonged hospital stay unrelated to the worsening of adverse events is not a serious adverse event in itself, such as:

- Admission due to pre-existing disease without new adverse events or worsening of pre-existing disease (e.g., laboratory abnormalities that persist since the time of study initiation);
- Managed reasons for hospitalization (e.g., annual routine physical examinations);
- Hospitalization during clinical study as specified in the study protocol (e.g., as required by the study protocol);
- Adolescent hospitalization unrelated to the deterioration of adverse events (e.g., elective cosmetic surgery);
- Pre-arranged treatments or surgical procedures should be recorded in the baseline data of the entire study protocol and/or the individual subject;
- Admission was due to the use of blood products.

Diagnostic or therapeutic invasive procedures (such as surgery) and non-invasive operations should not be reported as adverse events. However, when the underlying medical condition necessitating such procedures meets the definition of an adverse event, they must be reported. For example, acute appendicitis occurring during the adverse event reporting period should be classified as an adverse event, while the subsequent appendectomy performed for this condition should be recorded as the treatment method for that adverse event.

(6) Reporting procedures for SAE

The reporting period for serious adverse events (SAEs) should commence from the date of subject's informed consent and continue until 30 days after the final medication administration, inclusive of the 30th day. During the trial, if an SAE occurs − whether in initial reports or follow-up communications − investigators must immediately complete the Serious Adverse Event Report Form, sign it with the date, notify the sponsor within 24 hours of receiving the SAE, and report to relevant authorities as required by regulations.

Severe adverse events should be thoroughly documented with detailed records of symptoms, severity levels, occurrence time, intervention timing, implemented

measures, follow-up schedules and methods, clinical outcomes, and their relationship to treatment. If the intensity of an ongoing severe adverse event or its connection to treatment changes, the sponsor must be immediately notified through follow-up reporting. All severe adverse events should be monitored until full recovery or stabilization is achieved.

8.5 Recording of adverse events

Document all adverse events (AEs) during the study period in detail, including their names, severity levels, occurrence timing, duration, management measures, clinical outcomes, and relationship to treatment. These records must be accurately documented in the Case Report Form (CRF). Abnormal laboratory test results should be recorded on the CRF and followed up with at least one repeat test per week until normalization or study completion. All adverse events occurring within 28 days after the final medication administration must be reported and documented.

9. Statistics

9.1 Statistical analysis data set

Full Analysis Set (FAS): Following the intention-to-treat (ITT) principle, this analysis evaluates treatment efficacy for all randomized participants who received at least one medication dose. For cases with incomplete treatment data, the last observed data (LOCF) is applied to the final trial outcomes.

Protocol-compliant cases: All cases that comply with the trial protocol, demonstrate good adherence, do not use prohibited medications during the trial period, and complete the required content in the Case Report Form. No data imputation is performed for missing information. Both FAS and PPS are statistically analyzed to evaluate drug efficacy.

Safety Analysis Set (SAS): All enrolled cases, all patients who have used the trial drug at least once and have a post-treatment safety record, are included in the safety analysis set. This data set is used for safety analysis.

9.2 Statistical analysis methods

Unless otherwise specified, all data will be summarized by treatment group using appropriate statistical measures for each data type: Numerical data will be described using mean (Mean), standard deviation (STD), median (Median), minimum (Minimum), and maximum (Maximum); Categorical data will be presented as frequency (Frequency) and percentage (Percentage). For time-to-event data, the Kaplan-Meier (KM) survival analysis will estimate median survival time. When necessary, survival curves will be plotted with 95% confidence intervals for median time to events.

9.3 Analysis of efficacy endpoints

Primary endpoint of efficacy:

Progression-free survival (PFS): Kaplan-Meier method was used to analyze PFS, estimate median PFS and 95%CI, and draw survival curve

Secondary endpoints were:

Objective response rate (ORR, based on RECIST v1.1 criteria): percentage of subjects with complete response (CR) and partial response (PR) in the total analysis set and its 95% CI.

Disease Control Rate (DCR): percentage of subjects with complete response (CR), partial response (PR), and disease stabilization (SD) in the total analysis set and its 95% CI;

Relief duration (DOR): Statistical analysis of DOR using Kaplan-Meier method to estimate median DOR and 95%CI;

Overall survival (OS): Statistical analysis of OS using Kaplan-Meier method to estimate median OS and 95%CI;

9.4 Adverse event analysis

This study primarily employs descriptive statistical analysis to systematically document adverse events and reactions (defined as "adverse events with a 'definitely related, likely related, or possibly related' association to the investigational drug") observed during the trial. Laboratory test results are described to examine pre-trial normality that became abnormal post-treatment, along with the correlation between

these abnormalities and the investigational drug. Chi-square tests were conducted to evaluate the incidence rates of adverse reactions across different stratified groups.

10 Quality control and test records

10.1 Data quality assurance

The testing center shall establish an internal quality assurance system to strictly monitor and control the quality of its laboratory tests. The center must ensure the accuracy and reliability of test results, with standardized criteria for interpreting abnormal values. All relevant laboratory data should be promptly and accurately recorded in CRFs, and original reports or copies must be attached to medical records. Abnormal data must be verified, with relevant researchers providing explanations when necessary. Follow-up tracking should continue until the data normalize or stabilize.

10.2 Test records

All trial data are documented in the Case Report Form (CRF). Investigators are responsible for recording trial data on CRF in a timely, accurate, complete, authentic, and legally compliant manner, ensuring consistency with original records. All errors or omissions have been corrected or marked, and are signed by the investigator with a date.

11.2.1 Original records

Original records serve to verify the authentic existence of subjects and ensure data integrity and authenticity. All data recorded on CRFs originate from original documentation and must remain consistent with these records. Where discrepancies exist between CRF entries and original records, corrections should be made according to the original documentation or reasonable explanations provided. Original records are stored at each clinical trial center. The following documents are included in the original records:

- Laboratory test report of this center;
- Other medical examination data of the subject;
- The discharge summary of the subject.

10.2.2 Access to raw data and files

In addition to the investigator, personnel related to the trial, members of the ethics committee and personnel of the pharmaceutical administration agency have the right to access the original data and documents related to the trial. When the above personnel request to access the trial documents, the investigator shall provide complete information.

10.2.3 Preservation of test records

To ensure proper evaluation and supervision by the ethics committee and sponsor, the trial center must maintain all relevant clinical trial documentation in compliance with Good Clinical Practice (GCP) requirements. This includes identity-verification documents (such as original signed informed consent forms, Case Report Forms [CRFs], and original medical records), along with distribution/recovery records for investigational drugs. All trial-related materials shall be retained for five years following the completion of the clinical trial.

10.3 List reporting and rapid reporting of adverse events

Reports of adverse events can be classified as list reports and rapid reports according to severity.

The adverse events reported in the list are common general adverse events and do not require urgent treatment.

The investigator shall immediately report to the sponsor and the drug manufacturer (within 24 hours of SAE awareness) any serious adverse events that occur during the trial, and recommend reporting to the GCP Center safety officer (as required by the center), followed by timely follow-up and summary reports.

10.4 Breach of test protocol

The investigator/assistant investigator shall keep a detailed record of any protocol violations that occur during the trial and submit it to the principal investigator at the center and the sponsor, stating whether the behavior was caused by the elimination of potential harm to the subject or other unavoidable medical reasons.

11 Ethics Information and Confidentiality Agreement

This trial is conducted in compliance with the Chinese Good Clinical Practice (2020 Edition) and the Helsinki Declaration (2013 Edition). In accordance with standard medical practice, investigators are responsible for diagnosing and treating participants. Should any urgent safety issues arise during the trial, or if serious violations of the protocol, Good Clinical Practice (GCP), or the Helsinki Declaration occur, investigators must immediately notify their collaborating partners to ensure participant safety.

11.1 Ethics approval and informed consent

Prior to initiating a clinical trial, all documents including the study protocol and informed consent forms must be reviewed and approved by the ethics committee of the responsible institution. Investigators are required to report any progress of the trial and serious adverse events occurring during the trial to the ethics committee. Any modifications to the study protocol or informed consent forms must be submitted to the ethics committee for review and approval. Before enrolling participants, investigators must fully explain the purpose, procedures, and potential risks/benefits of the trial to the participants (or their guardians in special circumstances). Participants must be informed of their right to withdraw at any time. Each participant (or guardian in special circumstances) must sign an informed consent form before enrollment. Investigating physicians must obtain signed, dated, and contact information-based informed consent forms from all participants prior to study entry. The original copy shall be archived at the institution as trial documentation, while copies are provided to participants for retention. Any modifications to the informed consent form must be documented and submitted to the ethics committee for review and approval. Approved revised versions of the informed consent form must also be archived at the institution. All patients or independent witnesses affected by changes to the informed consent form, as well as individuals involved in discussions about the form, must sign and date the updated version. The original copy remains archived at the institution, while copies are provided to participants for retention.

11.2 Confidentiality Agreement

All materials, information (oral or written), and unpublished documents provided by the investigator—including the study protocol and CRF—shall remain the investigator's exclusive property. Without the investigator's prior written consent, no individual may disclose such materials to unauthorized personnel. Except for information permitted by regulations, the investigator must maintain confidentiality regarding all information received, obtained, or derived during this research process, taking all necessary steps to ensure confidentiality is maintained.

12 Programme revisions

Any revisions to the protocol will be documented in a written version signed by the investigator. The signed version will be attached to this protocol. Any revisions to this protocol may require submission in accordance with local regulations.

13. Results published

13.1 Ownership and use of research data and findings

The data shall not be used without the permission of the partner. The Scientific Committee has full access to the final data to enable proper academic analysis and reporting of the results.

13.2 Data dissemination

The publication or release of the results of the trial in a paper or conference shall be negotiated between the researcher and the partner. The researcher shall not disclose the results of the trial in any form without the written consent of the partner.

All participating researchers and committee members have granted full authorization to the Scientific Committee for the initial publication of research findings. No other publications are permitted prior to the initial release. Any subsequent publications by study participants (including sub-studies) must be

approved by the Scientific Committee and must reference both this study and its initial publication.

The parties may delay the publication or communication for a limited period of time, in order to protect the confidentiality or ownership of any information contained therein.

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Appendix 1. NCI CTCAE v5.0

Partial Common Toxicity Criteria (CTC) classification (5.0) from the National Cancer Institute (NCI)

For the full criteria, please refer to NCI CTCAE v5.0 or the following online information from the NCI website:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Appendix 2. Criteria for the evaluation of efficacy in solid tumors 1.1 Edition

1 Measurability of the tumor at baseline level

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be classified as measurable or non-measurable according to the following definitions:

1.1.1 Measurable lesions

Tumors: At least one measurable diameter (recorded as the maximum diameter) with a minimum length of:

- CT scan 10 mm (CT scan layer thickness not greater than 5mm)
- Clinical routine examination instrument 10 mm (if the tumor lesion can not be accurately measured by the measuring instrument, it should be recorded as unmeasurable)
- Chest X-ray 20 mm
- Malignant lymph node: Pathologically enlarged and measurable, the short diameter of a single lymph node on CT scan must be ≥15 mm (the recommended thickness of CT scan layer is not more than 5 mm). In baseline and follow-up, only the short diameter is measured and followed up.

1.1.2 Non-measurable lesions

All other lesions, including small ones (maximum diameter <10 mm or pathological lymph nodes with short diameters ≥ 10 mm to <15 mm) and those that cannot be measured. Unmeasurable lesions include: meningeal diseases, ascites, pleural or pericardial effusions, inflammatory breast cancer, cutaneous/pulmonary carcinomatous lymphangitis, imaging-uncertain abdominal masses requiring follow-up, and cystic lesions.

1.2 Description of measurement method

1.2.1 Focal measurements

During clinical evaluation, all tumor measurements should be recorded in metric meters. All baseline assessments of tumor lesion size should be performed as close as

possible to the start of treatment and must be completed within 28 days (4 weeks) prior to the start of treatment.

1.2.2 Evaluation method

Baseline assessment and follow-up measurements of lesions should be performed using the same techniques and methods. All lesions must be evaluated by imaging except those that cannot be evaluated by imaging and only by clinical examination.

Clinical Lesions: A lesion is considered measurable only when superficial and measuring ≥10 mm in diameter (e.g., skin nodules). For patients with skin lesions, it is recommended to archive color photographs containing a ruler for measuring lesion size. When both imaging and clinical evaluations are used, imaging should be preferred as it provides greater objectivity and allows for repeated review at the conclusion of research.

Chest X-ray: When tumor progression is an important research endpoint, chest CT should be prioritized because CT is more sensitive than X-ray, especially for new lesions. Chest X-ray is only applicable when the lesion boundary is clear and the lung ventilation is good.

CT and MRI: CT remains the gold standard for efficacy evaluation due to its superior repeatability. This guideline defines measurability based on CT scans with a thickness ≤5 mm. For areas thicker than 5 mm, lesions should be at least twice as thick to achieve measurable results. MRI may also be acceptable in specific scenarios, such as whole-body scans.

Ultrasound: Ultrasound should not be used as a measurement method for assessing lesion size. Due to its operational dependency, ultrasound examinations lack repeatability after measurement, and cannot ensure technical consistency or measurement uniformity across different measurements. If new lesions are detected during testing using ultrasound, CT or MRI should be employed for confirmation. When considering radiation exposure risks associated with CT scans, MRI may serve as an alternative.

Endoscopy, laparoscopy: These techniques are not recommended for objective evaluation of tumors, but they can be used to confirm CR in biopsy specimens obtained and to confirm recurrence in trials where the study endpoint is CR followed by recurrence or surgical resection.

Tumor markers: While tumor markers cannot be used alone to assess objective tumor response, baseline levels exceeding normal ranges must return to normal

thresholds for complete response evaluation. Given that marker levels vary by disease type, these factors should be considered when establishing measurement criteria in clinical protocols. Specific criteria for CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published. Furthermore, the International Gynecologic Cancer Organization has developed CA-125 progression criteria that will soon be incorporated into the objective evaluation standards for first-line ovarian cancer treatment regimens.

Cytological/Histological Techniques: In specific scenarios outlined in the protocol, these techniques can be employed to differentiate between Progressed Relapse (PR) and Cured Relapse (CR) (for example, residual benign tumor tissue is frequently observed in germ cell tumors). When exudates may indicate potential side effects of therapy (such as treatment with taxane compounds or angiogenesis inhibitors), and when measurable tumor response meets remission or disease stabilization criteria, the presence or exacerbation of tumor-associated exudates during treatment can be confirmed through cytological analysis. This approach helps distinguish between clinical responses (or stable disease status) and disease progression.

2. Tumor response assessment

2.1 Assessment of all tumors and measurable lesions

To evaluate objective response or potential future progression, it is essential to conduct baseline assessment of tumor burden in all lesions as a reference for subsequent measurements. In clinical trials with objective response as the primary endpoint, only patients with measurable lesions at baseline are eligible for enrollment. Measurable lesions are defined as those containing at least one detectable lesion. For studies targeting disease progression (measured over time or at fixed intervals), the eligibility criteria must explicitly specify whether participants with measurable lesions or those without measurable lesions are eligible.

2.2 Baseline records of target and non-target lesions

When there are more than one measurable lesions during baseline evaluation, all lesions should be recorded and measured, with a total of no more than 5 lesions (no more than 2 per organ), as the target lesions represent all involved organs (that is, a patient with one or two cumulative organs can choose a maximum of two or four target lesions as baseline measured lesions).

Target lesions must be selected based on size (longest diameter), represent all involved organs, and measurements must be well reproducible. Sometimes a new,

repeatable maximum lesion may be selected when the largest lesion cannot be measured repeatedly.

Lymph nodes require special attention as normal tissues that can be detected on imaging even without tumor metastasis. Pathological lymph nodes defined as measurable nodules or target lesions must meet the following criteria: CT-measured short diameter ≥ 15 mm. Baseline measurements only require short diameter assessment. Radiologists typically use the short diameter to determine whether a nodule has undergone tumor metastasis. Nodule size is generally represented by two-dimensional imaging data (CT uses axial planes, while MRI selects one plane from axial, sagittal, or coronal views). The minimum value is taken as the short diameter. For example, a 20 mm× 30 mm abdominal nodule with a short diameter of 20 mm can be considered malignant and measurable. In this case, 20 mm represents the measured value. Nodules measuring ≥10 mm but <15 mm should not be regarded as target lesions. Nodules smaller than <10 mm do not fall under the category of pathological nodes and need neither documentation nor further observation.

The total baseline diameter is calculated as the sum of all target lesion diameters (including the maximum diameter of non-nodular lesions and the minimum diameter of nodular lesions). If lymph node diameter is included, only the minimum diameter will be counted, as mentioned above. This baseline diameter total serves as a reference value for assessing disease baseline levels.

All other lesions, including pathological lymph nodes, are considered non-target lesions and do not require measurement. However, they should be documented during baseline evaluation, such as when recorded as "present," "absent," or in rare cases "confirmed progression." Extensive target lesions may be combined with target organ records (e.g., multiple enlarged pelvic lymph nodes or extensive liver metastases).

2.3 Mitigation criteria

2.3.1 Target lesion assessment

Complete remission (CR): all target lesions are absent and the short diameter of all pathological lymph nodes (including target and non-target nodules) must be reduced to <10 mm.

Partial response (PR): a reduction of at least 30% in the sum of the diameter of the target lesions compared to baseline levels.

Progression (PD): The minimum value of the sum of all measured lesion diameters throughout the study is used as the reference. Disease progression is confirmed when the diameter and relative increase reach at least 20% (using baseline measurements as reference if baseline values are available). Additionally, an absolute increase of at least 5 mm in the total diameter (including the presence of new lesions) must be met.

Stable disease (SD): the degree of reduction of the target lesion is not up to PR, and the degree of increase is not up to PD level, between the two. During the study, the minimum value of the sum of diameters can be used as a reference.

2.3.2 Evaluation of non-target lesions

This section defines the criteria for response to non-target lesions. Although some non-target lesions are actually measurable, they do not need to be measured and only qualitative assessment is required at the time points specified in the protocol.

Complete response (CR): All non-target lesions are eliminated and tumor markers return to normal levels. All lymph nodes are non-pathological in size (shorter than 10 mm).

Non-completion/non-progression: presence of one or more non-target lesions and/or sustained tumor marker levels beyond normal levels.

Disease progression: There is clear progression of existing non-target lesions. Note: The presence of one or more new lesions is also considered disease progression.

2.3.3 New lesions

The emergence of new malignant lesions signals disease progression, making their evaluation crucial. While no specific imaging criteria exist for detecting new lesions, their identification should be clearly established. For instance, disease progression cannot be attributed to variations in imaging techniques, morphological changes in imaging, or other pathological conditions (such as so-called new bone lesions being merely cured or recurrent cases of the original lesion). This is particularly important when partial or complete response is observed in baseline lesions. A case in point: necrosis of a liver lesion might be reported as a new cystic lesion on CT scans, but it may not actually represent a new occurrence.

Lesions detected during follow-up but not identified in baseline evaluations are considered new lesions and indicate disease progression. For example, if a patient with visceral lesions detected at baseline develops metastatic lesions on subsequent cranial CT or MRI scans, these intracranial metastases would be recognized as evidence of

disease progression, even if the patient had not undergone cranial imaging during their initial evaluation.

If a new lesion is not clearly identified, such as due to its small size, further treatment and follow-up evaluation are required to confirm whether it is a new lesion. If repeated examinations confirm that it is a new lesion, the time of disease progression should be calculated from the time of initial detection.

2.4 Best overall efficacy evaluation

The best overall response is defined as the optimal therapeutic outcome recorded from the start to the conclusion of a clinical trial, with all necessary conditions being considered for confirmation. Since responses may persist beyond treatment completion, protocols must specify whether post-treatment evaluations are included in this assessment. The protocol should clearly define how new therapies administered prior to disease progression affect the overall response. A patient's best response depends on outcomes from both target and non-target lesions, along with manifestations of new lesions. Additionally, it relies on the study design, protocol requirements, and outcome metrics. Specifically, in non-randomized trials, response status becomes the primary objective, with confirmation of partial response (PR) or complete response (CR) being mandatory to establish the best overall response.

2.4.1 Point-in-time response

Assuming that therapeutic responses occur at specific time points in each protocol, Table 1 will provide a summary of the overall therapeutic response at each time point in a patient population with measurable disease at baseline levels.

If the patient has no measurable lesion (no target lesion), the evaluation can be seen in Table 2.

2.4.2 Best overall relief: all time points

Once all the patient's data is available, the best overall response can be determined.

Evaluation of Best Overall Response (BOR) in Studies Not Requiring Confirmation of Complete or Partial Efficacy: The best response in a trial is determined by the highest response observed across all time points. For example, a patient may achieve SD in the first cycle, PR in the second cycle, and PD in the final cycle, yet still be evaluated as having PR for BOR. When BOR is assessed as SD, the patient must meet the protocol-specified minimum duration from baseline. Failure to meet this minimum duration renders any BOR evaluation of SD invalid, with subsequent assessments determining the BOR status. For instance, a patient who achieves SD in

the first cycle and PD in the second cycle but fails to meet the SD minimum duration requirement would be evaluated as PD for BOR. Similarly, a patient who achieves SD in the first cycle but becomes untraceable will be considered non-evaluable.

Evaluation of Best Overall Response (BOR) in Studies Requiring Confirmation of Complete or Partial Efficacy: A complete or partial response can only be declared when all participants meet the trial's partial or complete remission criteria, and subsequent efficacy confirmation is specifically requested at a later time point (typically four weeks post-treatment). The definition of BOR in this context is detailed in Table 3.

Table 1 Response at time points: subjects with target lesions (including or excluding non-target lesions)

Target lesion	Non-target lesions	New lesions	Overall relief
CR	CR	mistake	CR
CR	Non-CR/non-PD	mistake	PR
CR	Can not evaluate	mistake	PR
PR	Non-progression or incomplete assessment	mistake	PR
SD	Non-progression or incomplete assessment	mistake	SD
Can not be fully assessed	Non-progress	mistake	NE
PD	Any circumstances	Yes or no	PD
Any circumstances	PD	Yes or no	PD
Any circumstances	Any circumstances	yes	PD
CR= complete remission	PR= partial remission	SD= disease stable	PD= PD NE= Not assessable

Table 2 Response at time points-subjects with only non-target lesions

Non-target lesions	New lesions	Overall relief
CR	mistake	CR
Not CR or PD	mistake	Not CR or PD
Can not be fully assessed	mistake	Can not evaluate

PD that can not be clearly identified	Yes or no	PD
Any circumstances	yes	PD

Note: For non-target lesions, "non-CR/non-PD" refers to response better than SD. Since SD is increasingly being used as an endpoint for evaluating treatment efficacy, the definition of non-CR/non-PD was established to address the unmet need for measurable lesion-free status.

For unclear progression findings (e.g., very small new lesions of uncertain nature; cystic changes or necrotic lesions in existing lesions), treatment may continue until the next evaluation. If disease progression is confirmed during the next evaluation, the date of progression should be recorded as the date when the suspected progression was first observed.

Table 3 Best overall response required to confirm CR and PR efficacy

The first time point showed total remission	Then the total time to remission	Best overall relief
CR	CR	CR
CR	PR	SD, PD or PRa
CR	SD	If the SD lasts long enough, it is SD; otherwise, it should be PD
CR	PD	If the SD lasts long enough, it is SD; otherwise, it should be PD
CR	NE	If the SD lasts long enough, it is SD; otherwise, it should be NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	If the SD lasts long enough, it is SD; otherwise, it should be PD
PR	NE	If the SD lasts long enough, it is SD; otherwise, it should be NE

NE	NE	NE

Note: CR denotes complete response, PR indicates partial response, SD signifies disease stabilization, PD represents disease progression, and NE stands for non-evaluable. Superscript "a" applies when true CR is achieved at the first time point. If any disease reappears at subsequent time points, even if meeting PR criteria relative to baseline, the efficacy evaluation will remain PD in later stages (as disease reemerges after CR). The best response is determined by whether SD occurs within the shortest possible treatment interval. However, cases where initial CR is followed by subsequent scans showing residual lesions may require revision. In such instances, the initial CR should be revised to PR, while the best response should be classified as PR.

2.6. Efficacy evaluation/Confirmation of remission

2.6.1. Confirmation

For non-randomized clinical studies with primary endpoints focused on therapeutic efficacy, it is essential to confirm the effectiveness of Partial Response (PR) and Complete Response (CR) to ensure these outcomes are not due to evaluation errors. This requirement also allows reasonable interpretation of results when historical data are available, though such data must have undergone prior validation. However, in all other scenarios—such as randomized trials (Phase II or III) or studies with primary endpoints targeting disease stabilization or progression—therapeutic confirmation becomes unnecessary as it holds no value for interpreting trial outcomes. The removal of this requirement, however, makes central review to prevent bias particularly crucial, especially in non-blind experimental studies.

In the case of SD, at least one measurement in line with the SD criteria specified in the protocol shall be made within the shortest possible interval after the start of the test (generally not less than 6 to 8 weeks).

2.6.2 Total remission period

The total remission period is defined as the time from the first measurement meeting the criteria for CR or PR (whichever was achieved first) to the first documented recurrence or disease progression (with the minimum measurable value recorded during the trial serving as the reference for disease progression). The total complete response period refers to the duration between the initial measurement meeting CR criteria and the first confirmed recurrence or disease progression.

2.6.3. Disease stable phase

The disease progression time is defined as the duration from treatment initiation to disease progression (in randomized trials, starting from randomization). The minimum total sum observed in the trial serves as a reference point (if baseline totals are minimal, this serves as the basis for PD calculation). The clinical significance of disease stabilization periods varies across studies and diseases. When a specific trial uses the proportion of patients maintaining the shortest stabilization period as its primary endpoint, the protocol must explicitly specify the minimum interval between measurements in the stabilization period definition.

Note: The impact of follow-up frequency during remission, stable disease, and progression-free survival (PFS) after baseline evaluation should be considered. The definition criteria for follow-up frequency are not within the scope of this guideline. Follow-up frequency should take into account multiple factors such as disease type and stage, treatment duration, and standard protocols. However, when conducting inter-experiment comparisons, limitations in the accuracy of these endpoints must be addressed.

Appendix 3. Relationship between adverse events and investigational drug

The relationship between adverse events and the test drug was evaluated according to the 5-level classification standard of "definitely related, probably related, undetermined, probably unrelated, definitely unrelated", and the three items of "definitely related, probably related and undetermined" were combined to be considered as adverse reactions. The incidence of adverse reactions was calculated accordingly (see the table below for details).

Criteria for judging the causal relationship between adverse events and drugs

metric	Must be related	Probably relevant	Can not decide	It may not matter	It certainly doesn't matter
The time of AE occurrence coincides with the time of medication	+	+	+	+	-
AE and drug are known to have adverse reactions	+	+	+	-	-
AE improved or disappeared after discontinuation of the drug	+	+	±	±	-
AE occurred again after re-administration	+	?	?	?	-
The AE can not be explained by other causes	+	+	±	±	-

Appendix 4. ECOG Physical Status Rating Criteria

scoring	activity level
0	It's perfectly normal to be able to do all the normal things without any restrictions
1	No strenuous physical activity, but can walk and engage in light physical activity or office work
2	Can walk around and live on their own, but can not do any work, spend no more than 50% of the day in bed
3	Living a barely self-sufficient life, requiring bed rest or sitting in a chair for more than 50% of the day
4	Complete loss of mobility and severe inability to care for themselves, requiring bed or wheelchair
5	die