Randomized, double-blind, placebo-controlled, multicenter clinical study of camrelizumab combined with SRT/WBRT and chemotherapy in the first-line treatment of driver gene-negative non-small cell lung cancer patients with brain metastases

Protocol number: **CTONG2003/MA-NSCLC-III-009**
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Applicant: **Guangdong Association of Clinical Trials**

VERSION HISTORY/REVISION HISTORY

Documents	Version date	Explanation of the reasons for the modification and summary of the changes
V1.0	September 15, 2020	Not applicable
V1.1	October 26, 2020	The study design was changed to placebo-controlled. Amendment plan: • Modification of the overall description of the protocol • Statistical description modification
V2.0	May 12, 2023	Amendment plan: • Modification of the primary and secondary endpoints • Addition of patient-reported outcomes as exploratory endpoints • Updated description of inclusion and exclusion criteria • Statistical description modification

Contents

Research flow chart

Stage	Screening period		Treatment period (21 days per treatment cycle)		End of treatment [19] (Day -14 to Day 7	90-Day safety follow-up		Survival follow-up Every 3 months (±7 days)
	~Day -28~ to Day 1	~Day-7to Day 1	Cycle 1 Days 1-3	Subsequent cycle Day 1±3		Day 30±7	30n±7 (n=2, 3)	
Written informed consent [1]	X							
Inclusion/exclusion criteria, randomization[2]	X							
Demographics/smoking history/past medical history/previous medications [3]	X							
Driver gene detection [4]	X							
Vital sign examination [5]		X		X	X	X		
Weight and height measurement [6]	X			X	X	X		
Physical examination		X		X	X	X		
Comorbidities	X							
Symptoms of ICH [7]		X		X	X	X		
Eastern Cooperative Oncology Group (ECOG) Performance		X		X	X	X		

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	~Day -28~ to Day 1	~Day-7to Day 1	Cycle 1 Days 1-3	Subsequent cycle Day 1±3		Day 30±7	30n±7 (n=2, 3)	
Status scale score								
12-lead ECG [8]		X		X	X	X		
Routine blood test/blood biochemistry test/routine urine test/fecal occult blood test [9]		X		X	X	X		
Coagulation function test [10]		X		X	X	X		
Serum pregnancy test		X			X			
Echocardiography	X			Additional tests should be conducted if there are clinical indications.	X			
Cardiac enzyme profile [11]		X		Additional tests should be conducted if there are clinical indications.	X			
Thyroid function test [12]		X		Tests should be conducted once per cycle during cycles 2 to 4, and once every two cycles thereafter	X	X		
HPA axis function test [13]	X			Conditions permitting, tests should be conducted once per cycle during cycles 2 to 4, and	X			

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	~Day -28~ to Day 1	~Day-7to Day 1	Cycle 1 Days 1-3	Subsequent cycle Day 1±3		Day 30±7	30n±7 (n=2, 3)	
				once every two cycles thereafter.				
HIV, HBV, and HCV tests [14]	X							
Study medication			X	X				
Tumor imaging evaluation [15]	X		Assessed every 6 weeks (± 7 days) for the first 12 months after the first dose, and every 12 weeks (±7 days) thereafter		X	X*		
Assessment of cognitive function [16]		X		Performed at each imaging evaluation	X	X		
Quality of life scoring [17]		X		Performed at each imaging evaluation	X	X		
Evaluation of AEs			X	X	X	X	X	
Concomitant medications [18]	X	X	X	X	X	X	X	
Survival status						X	X	X
Subsequent antitumor therapy						X	X	X

Notes:

1. Based on the ethical principles of subject protection, the project agrees to use test results that meet the requirements of the protocol and can be traced at the center before the signing of informed consent.
2. Whenever possible, the subjects will receive the first dose of the study treatment on the day of randomization. If treatment cannot be administered on the day of randomization, treatment should start within three days after the randomization number is obtained.
3. Previous medications include treatment for the initial diagnosis such as chemotherapy, radiotherapy, and surgical treatment, and the time of the last antitumor

treatment must be recorded.

4. The research center must be able to provide relevant documentation on the patients' EGFR mutation and ALK gene rearrangement status. If the research center cannot provide these source documents, the subject should be reexamined.
5. Vital sign examinations will include body temperature, pulse, respiratory rate, and blood pressure. Subject blood pressure should be measured by the investigator during the screening period and before each planned camrelizumab/placebo infusion.
6. Height measurements will be taken only during the screening period. Body weight measurement will be required during the screening period, before each dosing, at the end of treatment, and during the safety follow-up.
7. Symptoms of intracranial hypertension (ICH) include nausea or vomiting (except for that caused by chemotherapy or cerebral infarction), headache, cognitive or emotional disorders, epilepsy, and limb movement disorders. Investigator judgment on the clinical status of the subject will be required during the screening period, before each planned camrelizumab/placebo infusion, at the end of treatment, and during the safety follow-up.
8. A 12-lead electrocardiogram (ECG) will be scheduled as follows: during the screening period, before each administration of camrelizumab/placebo, at the end of treatment, and during the safety follow-up.
9. Routine blood tests will include red blood cell (RBC) count, hemoglobin (HGB) concentration, hematocrit (HCT), white blood cell (WBC) count, platelet (PLT) count, and WBC differential [lymphocyte (LYM) count, absolute neutrophil count (ANC), monocyte (MONO) count, eosinophil (EOS) count, and basophil (BASO) count]. Blood biochemical indicators will include liver function indicators [serum total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (γ-GT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), and lactate dehydrogenase (LDH)]; renal function indicators [blood urea nitrogen (BUN)/urea (UREA) and creatinine (Cr)]; and blood electrolytes (Na, K, Cl, Mg, Ca, and P). Routine urine indicators will include pH, urine leukocyte (ULEU) count, urine protein (UPRO) level, urine red blood cell (URBC) count, and urine glucose (UGLU) level. Fecal occult blood test: If the test result is positive, the investigator will conduct a re-rest as appropriate. If the result remains positive, the investigator will perform a gastrointestinal endoscopy to rule out gastrointestinal bleeding based on clinical needs.
10. Coagulation function tests will include prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR). The

tests will be performed within 7 days before the first study dosing, before the administration of camrelizumab/placebo on day 1 of each cycle, at the end of treatment, and during the safety follow-up.

11. Cardiac enzyme profile will include phosphocreatine kinase (CK) and creatine kinase-MB (CK-MB). The test will be performed once within 7 days before the first study dosing. The test will be subsequently performed only when symptoms such as precordial pain, palpitations, and ECG abnormalities occur.
12. Thyroid function tests will include triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH). Thyroid function tests will be conducted during the screening period, in each of cycles 2-4, on the first day of every two subsequent cycles before the administration of camrelizumab/placebo, at the end of treatment, and during the safety follow-up.
13. Hypothalamic–pituitary–adrenal (HPA) axis function tests will include corticotropin-releasing hormone (CRH) (hypothalamus), adrenocorticotropic hormone (plasma ACTH) (pituitary), and cortical hormones (adrenal glands). The measured adrenal cortical hormones will include serum cortisol, urine free cortisol (UFC), urine 17-ketosteroids (17-KS), and urine 17-ketosteroids (17-KGS). In hospitals where conditions permit, monitoring is recommended during the screening period, in each of cycles 2-4, and on the first day of every two subsequent cycles before the administration of camrelizumab/placebo. (Hospitals lacking appropriate conditions may test only some of the indicators or may not perform routine visit tests.)
14. This includes hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) antibody tests. For HBV testing, it will be required to test hepatitis B surface antigen (HbsAg) (qualitative), hepatitis B surface antibody HbsAb (qualitative), hepatitis B core antibody (HbcAb) (qualitative), hepatitis B e-antigen (HbeAg) (qualitative), hepatitis B e-antibody HbeAb (qualitative), and/or HBV-DNA (quantitative) during the screening period. For HCV, it will be required to test HCV-Ab during the screening period to determine whether HCV infection is present; if positive, HCV-RNA (quantitative) will be measured. For HBV carriers to participate in the study, the investigator should arrange antiviral treatment as appropriate.
15. The methods used for tumor imaging evaluation in the baseline period must be the same as those used in each follow-up evaluation. Computed tomography (CT) or magnetic resonance imaging (MRI) scan is recommended, and MRI scan will be used for intracranial lesions. Other involved sites will be examined as prompted by each subject’s signs and symptoms. Baseline imaging must include the chest, upper abdomen, brain, and all known or suspected disease sites. Bone scans will be performed only when bone metastasis is clinically suspected. If relevant information was archived within 42 days before the first

administration, repeated scans will not be necessary. Each subsequent clinical tumor imaging evaluation should include the chest, brain and upper abdomen. The investigator may increase the frequency of imaging monitoring as needed. The baseline tumor evaluation will be performed within 28 days before the first dose. The imaging data obtained before providing informed consent can be used in tumor evaluation during the screening period if they meet the requirements of the protocol. Tumor evaluation will conducted once every 6 weeks (±7 days) within 12 months of the first dosing and once every 12 weeks (±7 days) thereafter until radiographic progressive disease (PD) is recorded. For subjects with the first recorded remission (complete remission [CR] or partial remission [PR]) or unconfirmed radiographic PD, it is recommended to reconfirm remission and PD after no less than 4 weeks. If PD is not confirmed, subjects will continue receiving study treatment and undergo imaging evaluation until PD is confirmed, in which case the treatment must be terminated. X*: For those who stop treatment for reasons other than PD imaging findings, imaging evaluation should continue following the image assessment schedule until any of the following events occurs: initiation of a new antitumor treatment, PD, or subject withdrawal of informed consent and/or death.

16. Neurocognitive function assessments will include the Mini-Mental State Examination (MMSE) scale and the Hopkins Verbal Learning Test-Revised (HVLT-R) scale. These will be completed by the investigator through interactions with the subjects at each visit. The baseline assessment should be completed before the first dose, followed by evaluations during each imaging assessment, at the end of treatment, and during the safety follow-up. The investigators should try their best to complete the above two scale assessments and record reasons for any incomplete scales.
17. Quality of life will be evaluated using the European Organisation for the Research and Treatment of Cancer (EORTC) Core 30-Item Quality of Life questionnaire (QLQ-C30) and the EORTC Quality of Life–Brain Neoplasm (QLQ-BN20) scales. The subjects will complete an evaluation before dosing, once during the screening period, once at each imaging assessment, once at study exit, and once during the safety follow-up 30 days later.
18. The combined medications and concomitant treatments should be recorded during the period from within 14 days before the first dosing (not less than this time) to the end of the safety follow-up period. If the subjects start other new antitumor treatments before the end of the safety follow-up, only the combined medication and concomitant treatment related to the study drug or fatal adverse events (AEs)/serious adverse events (SAEs) will be collected after the new antitumor treatment is initiated, and the combined medication and concomitant treatment for SAEs related to the study drug will be recorded after the safety follow-up.

19. At the end of treatment, routine blood tests, routine urine tests, fecal occult blood tests, blood biochemistry tests, coagulation function tests, pregnancy tests (if applicable), performance status tests, physical examinations, vital sign examination, and ECG examinations must be performed. Imaging examinations should be performed if imaging evaluation has not been conducted within 4 weeks before the end of treatment.

1. Research background

1.1 Epidemiological characteristics and current treatments of lung cancer with brain metastases

Lung cancer is the most common malignant tumor in China. Patients with advanced lung cancer often develop brain metastases. The incidence of brain metastases in lung cancer, which is the most common type of brain metastasis, is 23%-36%, and the prognosis is usually poor. Approximately 10%-15% of non-small cell lung cancer (NSCLC) patients have brain metastases at the time of diagnosis, and approximately 50% of patients could develop brain metastases during the disease course. Lung cancer patients with positive driver genes have a relatively high incidence of brain metastases [1- 2].

Many clinical trials have shown that immune checkpoint inhibitors (ICIs) can provide definite clinical benefits to patients with brain metastases. Preclinical data from brain tumor animal models suggest that cytotoxic T-lymphocyte associated protein 4 (CTLA-4) antibodies and programmed death (PD)-1 antibodies can cross the blood-brain barrier, thereby increasing the number of cluster of differentiation (CD)4+ T cells and decreasing the number of regulatory T cells (Tregs) [3]. In a study of 116 specimens of various malignant tumors with solitary intracranial metastasis, the authors reported that among 61 NSCLC patients, 26.2% expressed PD-L1, and more than 50% of the specimens contained the tumor-infiltrating lymphocytes (TILs) CD3, CD8, or CD45RO+. The degree of infiltration was closely related to brain tissue edema and patient prognosis. These cells have been identified as potential targets of ICIs in the microenvironment [4].

1.2 Efficacy of PD-1/PD-L1 drugs in patients with lung cancer with brain metastases

In recent years, due to the publication of a large amount of research data on the application of ICIs in the treatment of various tumors, ICIs have brought new hope for the treatment of patients with lung cancer with brain metastases. A comprehensive analysis of 971 patients in CheckMate 063, 017 and 057 showed that 46 patients with central nervous system (CNS) metastasis were treated with nivolumab, and 42 patients with CNS metastasis were treated with docetaxel. Patients with metastases who were asymptomatic, had stable CNS metastases, or developed CNS metastases after treatment; those who were free of neurological symptoms related to brain metastases for more than 2 weeks prior to enrollment; and those who had not received systemic corticosteroid therapy for more than 2 weeks prior to study treatment or less than 2 weeks before enrollment were included. Among patients receiving stable hormone doses, such as 10 mg of prednisolone, NSCLC patients with CNS metastases treated with nivolumab tended to exhibit improved overall survival (OS) [5]. In the OAK study, which included 425 patients, 38 patients who were asymptomatic and stable after previous local treatments were included in the atezolizumab treatment group, and 47 patients with brain metastases were included in the docetaxel group. Subgroup analysis suggested that atezolizumab treatment could reduce the risk of death compared with chemotherapy [6].

1.3 Timing of ICIs combined with radiotherapy in the treatment of lung cancer with brain metastases

This study will also include patients receiving a combination of intracranial radiotherapy (RT) and ICIs. The timing of RT intervention combined with ICIs in the treatment of lung cancer with brain metastases has been a focus of recent studies. A French multicenter, nonintervention, retrospective cohort study revealed that for NSCLC patients with brain metastases in whom first-line chemotherapy or beyond had failed and the PD-L1 expression level was unknown, patients who received RT $\leq$ 3 months prior to nivolumab treatment had higher intracranial remission than those who received RT $\geq$ 3 months prior to nivolumab treatment (30.0% vs. 6.7%), suggesting that the time window for RT combined with ICIs is relatively short [7].

1.4 Safety of ICIs combined with radiotherapy in the treatment of lung cancer with brain metastases

Although the existing data show that immunotherapy has potential efficacy benefits for NSCLC patients with brain metastases, immunotherapy may also cause fatal immune-related adverse reactions (irAEs) in the nervous system. A study published in JAMA Oncology in 2018 analyzed irAEs that occurred during treatment with CTLA-4 and anti-PD-1/PD-L1 antibodies in 7 medical centers in the United States and reported that approximately 15% of irAEs caused by anti-PD-1 and PD-L1 antibodies exhibited neurologic toxicity [8]. Moreover, three other retrospective studies suggested that the combination of immunotherapy and RT did not increase radionecrosis (RN). The overall safety of immunotherapy combined with RT is good, but whether this combination therapy increases RN is still debated [9] [10] [11].

ICIs have provided a new avenue for the treatment of patients with brain metastasis and have shown different degrees of beneficial effects in clinical trials and real-world studies. Immunotherapy combined with RT has shown good clinical benefits, but more studies are needed to clarify the population that could benefit most from combination therapy, the timing of combination therapy, and the prediction and treatment of adverse reactions (ARs). Most recent reports involve subgroup analyses in retrospective small-sample or prospective studies. Prospective, large, randomized controlled trials are needed to further determine the efficacy and safety of immunotherapy in patients with brain metastases.

2. Study drugs

2.1 Drug name and physicochemical properties

[Common name] Camrelizumab for injection
[Pinyin] Zhusheyong Karuilizhu Dankang
[English name] Camrelizumab for injection
[Active ingredient] Humanized anti-PD-1 monoclonal antibody
[Molecular weight] Approximately 146.3 kDa
[Properties] White to off-white powder or mass
[Specifications] 200 mg/bottle

2.2 Pharmacological type and mechanism of action

Camrelizumab is a humanized anti-PD-1 monoclonal antibody expressed in the Chinese hamster ovary (CHO) cell line via recombinant technology, contains 1314 amino acids and has a molecular weight of 143,708 Daltons. Camrelizumab is a heterotetramer containing two identical heavy chains (immunoglobulin G4) and two identical light chains (immunoglobulin κ). The drug specifically binds to PD-1, blocking the interaction between PD-1 and its ligand (PD-L1); this action terminates the immunosuppressive signal caused by the interaction between PD-1 and PD-L1 in T cells, restoring the immune response of T cells against the tumor.

3 Study objectives and observational indicators

3.1 Study objectives

Primary objective:

Progression-free survival (PFS) and intracranial PFS (iPFS) of driver gene-negative NSCLC patients with brain metastases receiving camrelizumab combined with stereotactic radiotherapy (SRT)/whole-brain radiotherapy (WBRT) and chemotherapy (as the first-line treatment) will be compared with those of patients receiving a placebo combined with SRT/WBRT and chemotherapy (as the first-line treatment) (investigator evaluation).

Secondary objectives:

1) PFS and iPFS (assessed by the central imaging evaluation team) and the intracranial objective response rate (iORR), ORR, intracranial duration of response (iDoR), DoR and OS will be compared between driver gene-negative NSCLC patients with brain metastases receiving camrelizumab combined with SRT/WBRT and chemotherapy

(as the first-line treatment) and those receiving placebo combined with SRT/WBRT and chemotherapy (as the first-line treatment).

2) The safety of camrelizumab combined with SRT/WBRT and chemotherapy as first-line treatment for driver gene-negative NSCLC patients with brain metastases will be compared with that of placebo combined with SRT/WBRT and chemotherapy.
3) The effects of camrelizumab combined with SRT/WBRT and chemotherapy on cognitive function in driver gene-negative NSCLC patients with brain metastases will be compared with those of placebo combined with SRT/WBRT and chemotherapy;

Exploratory objective:

Changes in patient-reported outcomes, such as the quality of life (QoL) scores (EORTC QLQ-C30, EORTC QLQ-BN20), from baseline will be compared between the experimental group and the placebo group.

3.2 Study endpoints

3.2.1 Primary endpoints

PFS and iPFS calculated according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (assessed by the investigator).

3.2.2 Secondary endpoints

1 Efficacy: PFS and iPFS (assessed by the central imaging evaluation team), iORR, ORR, iDoR, DoR, and OS.

2. Safety: incidence of treatment-related adverse events (AEs), abnormal laboratory test results and serious adverse events (SAEs) determined according to the NCI-CTCAE 5.0 standard.

3 Cognitive function: Changes in neurocognitive function before and after treatment with camrelizumab combined with chemoradiotherapy evaluated with the Mini-Mental State Examination (MMSE) and the Hopkins Verbal Learning Test-Revised (HVLT-R).

3.2.3 Exploratory endpoint

Patient-reported outcomes of changes in the QoL scores (EORTC QLQ-C30, EORTC QLQ-BN20) from baseline level and the remission of disease-related symptoms.

4 Study protocol

4.1 Study design

In this randomized, double-blind, placebo-controlled, multicenter clinical study, the efficacy and safety of camrelizumab combined with chemoradiotherapy as a first-line treatment for NSCLC patients with brain metastases will be evaluated. Subjects may voluntarily withdraw from the trial, and the investigators may remove subjects determined to be unsuitable for further trials. Each subject will be treated until the disease progresses or drug-induced side effects become intolerable, and then the subject will enter the survival follow-up period.

4.2 Study population

4.2.1 Sample size and power calculation

The primary endpoints of this study are iPFS and PFS, which are evaluated by investigators. In the BRAIN study [28], the iPFS of the control group (whole-brain RT ± chemotherapy) was 4.8 months. A pooled analysis of the KEYNOTE-021, KEYNOTE-189, and KEYNOTE-407 studies [29] revealed that the PFS in NSCLC patients with brain metastases treated with anti-PD-1 antibody in combination with chemotherapy was 6.9 months and that of patients receiving chemotherapy alone was 4.1 months, for an improvement of 2.8 months. Camrelizumab combined with chemoradiotherapy is expected to improve the median iPFS of subjects from 5 months reported in historical controls to 8 months (hazard ratio (HR)=0.625) while ensuring that the type I error does not exceed 0.05 (two-sided). PASS 21 software was used to calculate

the power and sample size as follows: at least approximately 153 iPFS events between both groups is needed to provide a power no less than 80% (approximately 81.8%) to detect differences in efficacy (in terms of iPFS) between the experimental group (camrelizumab combined with chemoradiotherapy) and the control group. The estimated enrollment time is 14 months, and the overall study period is 38 months. The full analysis set (FAS) will include at least 100 subjects in each group, for a total of at least 200 subjects. Under the assumption that camrelizumab combined with chemoradiotherapy can improve the median PFS of subjects from 4 months reported in historical controls to 7 months (HR=0.57), the enrollment of 100 subjects in each group can provide a power no less than 90% (approximately 92.8%) to detect differences in efficacy (in terms of PFS) between the experimental group and the control group.

4.2.2 Subject selection

Patients meeting the following criteria will be included in this study:

1) Age ≥18 years
2) Histologically or cytologically confirmed NSCLC
3) Brain parenchymal metastasis with ≥3 brain lesions confirmed by magnetic resonance imaging (MRI); metastasis with 1-2 brain lesions that are not suitable for or refuse surgical treatment; or metastasis with at least one brain lesion with a measurable diameter ≥5 mm with or without neurological symptoms and signs
4) No systemic treatment for advanced/metastatic NSCLC or chemotherapy and/or RT as a part of neoadjuvant/adjuvant therapy at least 12 months after the surgery when advanced or metastatic NSCLC was diagnosed
5) Presence of EGFR insensitive mutation detected in tumor tissue (or free tumor DNA in peripheral blood if tissue is difficult to obtain) by the ARMS method, Super ARMS method, Roche Cobas, droplet digital polymerase chain reaction (ddPCR), or next-generation sequencing (NGS) absence of ALK rearrangement confirmed by fluorescence in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-PCR), immunohistochemistry (IHC) using the Venata D5F3 platform, or NGS
6) Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
7) Good hematopoietic function, defined as an absolute neutrophil count ≥1.5×10^9/L, a platelet count ≥ 100×10^9/L, and hemoglobin ≥ 90 g/L [without blood transfusion or erythropoietin (EPO) dependency within 7 days]
8) Good liver function, defined as a total bilirubin level ≤ 1.5 times the upper limit of normal (ULN); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 2.5 times the ULN for patients without liver metastasis and ≤5 times the ULN for patients with recorded liver metastasis
9) Good renal function, defined as a serum creatinine level ≤ 1.5 times the ULN or a creatinine clearance (CrCl) ≥ 60 ml/min (calculated by the Cockcroft-Gault formula) and a urine protein level less than 2+ in a routine urine examination (if ≥ 2+, 24-hour urine protein level ≤1 g)
10) Good coagulation function, defined as an international normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 times the ULN or within the intended range for anticoagulant drugs for patients receiving anticoagulant therapy
11) Negative serum pregnancy test conducted within seven days before receiving the first dose of the study drug (cycle 1, Day 1) (female subjects with reproductive potential and male subjects with female partners of reproductive potential will be required to use a medically approved contraceptive method [e.g., intrauterine device (IUD), birth control pills, or condoms] for the course of the study and for at least 90 days after the last administration of the study drug)
12) Ability to comply with the study and follow-up procedures
13) Signed written informed consent.

Patients meeting any of the following criteria will be excluded in this study:

1) Brain metastases accompanied by hemorrhage
2) Meningeal metastasis
3) ROS1 mutations, positive RET fusions, BRAF V600E mutations, or positive NTRK fusions
4) Current participation in an intervention clinical study, receiving other study drugs or using the study device within 4 weeks before the first dose
5) Brain RT undergone before enrollment
6) Solid organ or blood system transplantation
7) Active autoimmune diseases that require systemic treatment (such as the use of disease-modifying drugs, corticosteroids or immunosuppressants) within 2 years before the first treatment (intermittent use of inhaled steroids or local injection of steroids is allowed; replacement therapy [such as thyroxine, insulin, or physiologic corticosteroids for adrenal or pituitary insufficiency] is not considered systemic treatment)
8) Immunodeficiency diagnosis or treatment with systemic glucocorticoids or any other form of immunosuppressive therapy that is not directly related to tumor treatment within 7 days before the first dose of the study drug (physiological doses of glucocorticoids is allowed [≤10 mg/day of prednisone or equivalent drugs])
9) History of noninfectious pneumonia requiring glucocorticoid treatment or current interstitial lung disease occurring within 1 year before the first dose
10) One of the following cardiac functions or diseases:
    - Arrhythmias that are clinically significant and obviously abnormal, including but not limited to complete left bundle branch block and second-degree atrioventricular block
    - QTc interval ≥450 ms in males and ≥470 ms in females as measured by 12-lead electrocardiography (ECG)
    - New York Heart Association (NYHA) grade ≥ 3 cardiac dysfunction or left ventricular ejection fraction (LVEF) <50% on cardiac color Doppler ultrasound examination
    - Myocardial infarction within 1 year before screening
11) Known history of human immunodeficiency virus (HIV) infection
12) Untreated active hepatitis B
    Note: Hepatitis B patients meeting the following criteria will not be excluded:
    a. Before the first dose, the HBV load must be <500 IU/ml or <1000 copies/ml. The investigator can decide whether to administer anti-HBV treatment during the study depending on the subject's condition.
    b. Subjects with anti-HBc(+), HBsAg(-), anti-HBs(-) and HBV viral loads(-) do not need to receive prophylactic anti-HBV treatment, but viral reactivation should be closely monitored.
13) Active HCV-infected subjects (positive HCV antibody and HCV-RNA levels above the lower limit of detection)
14) Serious infections (CTCAE ≥ grade 3), such as infectious complications requiring treatment, bacteremia, and severe pneumonia, within 4 weeks before the first treatment or signs and symptoms of infection requiring treatment with oral or intravenous antibiotics (excluding prophylactic antibiotic use) prior to first use of the study drug (NSCLC patients with lymphatic spread do not need to be excluded)
15) Pregnancy and breastfeeding
16) Known allergies to camrelizumab, pemetrexed/paclitaxel/albumin-paclitaxel, carboplatin/cisplatin or any of its excipients
17) Malignant tumors other than NSCLC within 5 years before randomization, except for adequately treated cervical carcinoma in situ (CCIS), basal cell or squamous cell skin cancer, local prostate cancer after radical mastectomy, and ductal carcinoma in situ after radical mastectomy.

4.2.3 Subject withdrawal criteria

1) Subjects who revoke their informed consent and ask to withdraw
2) Subjects who cannot tolerate drug toxicity
3) Subjects who are lost to follow-up or have positive blood human chorionic gonadotropin (HCG) levels
4) Subjects who are withdrawn from the study at the investigators' discretion

4.2.4 Study termination criteria

1) Unexpected, significant or unacceptable risks to the subjects are identified.
2) The study drug/treatment is not effective, or it is pointless to continue the trial.
3) The applicant decides to terminate the study for reasons such as severe lag in the enrollment of subjects or frequent protocol deviations.

4.3 Treatment regimen and dosage

4.3.1 Treatment regimen

The study will include a screening period (the time between the subjects signing the informed consent form and the first drug treatment will be no more than 28 days; imaging evaluations performed within 28 days before the first drug treatment and tumor tissue biopsies performed within 6 months before the first drug treatment will be included), a treatment period (treatment termination is defined as termination of treatment or withdrawal for any reason) and a follow-up period (including safety follow-up and survival follow-up).

Screening period:

The subjects are required to undergo a screening evaluation within 28 days before the first treatment to determine whether they are eligible for the study. Eligible subjects will be randomly divided into an experimental group and a control group at a ratio of 1:1. The experimental group will receive camrelizumab + pemetrexed/paclitaxel/albumin-paclitaxel + carboplatin/cisplatin ± SRT/WBRT. The control group will receive placebo + pemetrexed/paclitaxel/albumin-paclitaxel + carboplatin/cisplatin ± SRT/WBRT.

A stratified blocked randomization method will be used. In the randomized grouping, the following factors will be considered to balance the baseline data between the two groups: pathological classification (squamous cell carcinoma or nonsquamous cell carcinoma); number of intracranial metastatic lesions (1-5 or >5); and the presence or absence of RT. Treatment will be initiated within three days after the random drug number is determined.

Treatment period:

One dosing cycle will last 3 weeks, and drug treatment will be administered sequentially on the first day of each cycle. Beginning with the second cycle, the dosing time window can be ±3 days, but the subjects must undergo various examinations, including vital signs, physical examinations, laboratory examinations, and performance status scores, in addition to the imaging examination within 72 h before each dosing. The subjects will also undergo clinical tumor imaging evaluation once every 6 weeks (±7 days) within 12 months after the first administration and once every 12 weeks (±7 days) after 12 months (the evaluation method, computed tomography (CT) or MRI, will be consistent throughout the study).

Subjects with nonsquamous cell carcinoma randomly assigned to the experimental group will receive camrelizumab 200 mg + pemetrexed 500 mg/m^2 + carboplatin AUC 5/cisplatin 75 mg/m^2 ± SRT/WBRT; after 4-6 cycles of treatment, maintenance therapy of camrelizumab 200 mg + pemetrexed 500 mg/m^2 will be initiated. Subjects with nonsquamous cell carcinoma assigned to the control group will receive placebo + pemetrexed 500 mg/m^2 + carboplatin AUC 5/cisplatin 75 mg/m^2 ± SRT/WBRT; after 4-6 cycles of treatment, maintenance therapy of placebo + pemetrexed 500 mg/m^2 will be initiated.

Squamous cell carcinoma patients randomly assigned to the experimental group will receive camrelizumab 200 mg + paclitaxel 175 mg/m^2/albumin-paclitaxel 260 mg/m^2 + carboplatin AUC 5/cisplatin 75 mg/m^2 ± SRT/WBRT; after 4-6 cycles of treatment,

maintenance therapy of camrelizumab 200 mg will be initiated. Squamous cell carcinoma patients assigned to the control group will receive placebo + paclitaxel 175 mg/m^2/albumin-paclitaxel 260 mg/m^2 + carboplatin AUC 5/cisplatin 75 mg/m^2 ± SRT/WBRT; after 4-6 cycles of treatment, placebo maintenance treatment will be initiated.

If patients cannot tolerate chemotherapy even after more than 2 dose reductions, chemotherapy will be terminated, but camrelizumab/placebo treatment will be continued until one of the following situations occurs: disease progression, intolerable toxic side effects or death, comorbidities that affect further treatment, the investigator's decision to withdraw the subject from the study, noncompliance with the study treatment or study procedures, cumulative treatment time of more than 2 years, and other reasons specified in the protocol.

Subjects who terminate treatment or are withdrawn from the study will still be required to undergo a comprehensive examination, including vital signs, physical examination, laboratory examinations, QoL score, and clinical tumor imaging evaluation (CT or MRI).

Follow-up period:

Safety follow-up is required after the subjects are discharged from the study. The subjects will be followed up once every 30±7 days until 90 days. The first safety visit (30±7 days after discharge from the study) will be conducted in the research center and include examinations such as vital sign monitoring, physical examination, and laboratory examination; AEs, concomitant drugs, and concomitant treatments will be recorded and evaluated. The other two follow-up visits (60±7 days and 90±7 days after discharge) will be by telephone, and only survival information, AEs, concomitant drugs, and concomitant treatments will be collected.

After the safety follow-up period, the survival of the patients will be assessed by follow-up once every 3 months (±7 days) by telephone until death, loss to follow-up, withdrawal of informed consent, observation for 2 years, or termination of the study.

4.3.2 Dosage regimen

1) Camrelizumab/placebo dosing regimen: A 200 mg fixed-dose camrelizumab/placebo will be administered on Day 1 of each cycle. The dosing time window is ±3 days, but the subjects must complete all required clinical examinations and imaging examinations within 72 h before each dosing to evaluate the tolerance of the continued medication. It is recommended that the subjects be hospitalized for 72 h after the first dose. Camrelizumab/placebo will be intravenously infused for 30 min (no less than 20 min and no more than 60 min, including the washout phase). The intravenous drip will be passed through the medical infusion bag via an infusion set with an in-line filter (0.2 μM). This infusion pathway will not be used to administer other drugs before or after infusion.

2) Chemotherapy drug dosing regimens:

Pemetrexed for injection: One dosing cycle will last 3 weeks, and 500 mg/m^2 of pemetrexed will be administered on the 1st day of each cycle as an intravenous drip over 10 min.

Paclitaxel for injection (solvent-based): One dosing cycle will last 3 weeks, and 175 mg/m^2 of paclitaxel will be administered on the 1st day of each cycle via intravenous drip.

Paclitaxel for injection (albumin-bound): One dosing cycle will last 3 weeks, and 260 mg/m^2 of nab-paclitaxel will be administered on the first day of each cycle via intravenous drip.

Carboplatin for injection: One dosing cycle will last 3 weeks, and carboplatin (AUC 5) will be administered on the 1st day of each cycle as an intravenous drip (dehydration as needed).

Cisplatin for injection: One dosing cycle will last 3 weeks, and 75 mg/m^2 of cisplatin is administered on the 1st day of each cycle as an intravenous drip (dehydration as needed).

4.3.3 Radiotherapy regimen

The investigators will determine the need for intracranial RT based on the current guidelines and the patient's condition. During enrollment and randomization, the subjects will be stratified based on the presence/absence of an RT regimen. Subjects without a RT regimen will receive only the systemic treatment specified in the protocol; subjects who need

intracranial RT will undergo the following RT regimen:

The WBRT/SRT regimen should be completed within 42 days after the first treatment (camrelizumab/placebo + chemotherapy); if fractionated stereotactic radiotherapy (FSRT) is used, the first cycle of RT should be completed within 42 days after the first treatment (camrelizumab/placebo + chemotherapy). The recommended RT regimen is as follows:

WBRT regimen: 3 Gy of WBRT for each session, 5 times a week, for 2 weeks, with a total dose of 30 Gy or until the occurrence of intolerable ARs or intracranial progression.

SRT regimen: for single SRS, the recommended RT dose will be selected based on the maximum diameter of the intracranial lesions: ≤20 mm: 24 Gy; 21-30 mm: 18 Gy; and 31-40 mm: 15 Gy. FSRT will be used for tumors larger than 40 mm. For lesions adjacent to the brainstem ≤20 mm, the recommended RT dose is 16 Gy, and FSRT will be used for those larger than 20 mm.

During treatment, the investigator may make reasonable adjustments to the RT regimen based on the specific conditions of the patients and the recommendations of the current guidelines.

Various toxic side reactions may occur after RT in the CNS. For functional symptoms in the nervous system caused by acute radiation-induced brain edema, such as weakened limbs, dizziness, headache, nausea, and vomiting, the preferred treatment is dehydration (mannitol is recommended). Glucocorticoids may be for symptomatic treatment. For patients who require the use of glucocorticoids to reduce cerebral edema and control neurological symptoms, the recommended starting dose of glucocorticoids is dexamethasone (4-8 mg) or an equivalent dose of hydrocortisone, and the dose is reduced within 2 weeks after symptoms are controlled. The investigators may adjust the dose and frequency of dehydrating drugs and hormones based on clinical experience and guideline recommendations.

4.4 Bias reduction methods

4.4.1 Enrollment

This study is a randomized, double-blind, placebo-controlled study. After written informed consent is obtained, all screening procedures and evaluations are completed, and the eligibility of the subjects is determined, the IWRS will provide drug distribution information to the randomized subjects.

4.4.2 Randomization

Randomization is the main method for ensuring comparability between groups in this study. All personnel involved in the study will make every effort to ensure the strict implementation of the randomization plan.

This study will use the stratified blocked randomization method. The subjects who qualify for screening will be randomly assigned to the experimental group or the control group at a 1:1 ratio.

Randomized stratification will be performed according to the following factors:

Pathological type: squamous cell carcinoma/nonsquamous cell carcinoma

Number of intracranial metastatic lesions: 1-5, >5

RT regimen: with/without

The subjects in this study will be randomized using the RTSM system. The screened qualified subjects will be randomly assigned to the experimental group and the control group at a ratio of 1:1, and the corresponding drug number will be obtained through the RTSM system before the drugs are distributed. Whenever possible, the subjects will receive the first dose of the study drug on the day of randomization. If patients are unable to receive treatment on the day of randomization, treatment will be started within three days after the drug number is obtained.

Subjects who do not meet the study inclusion criteria will not be randomized under any situation. If a subject who does not meet the study inclusion criteria is randomized or receives

the incorrect treatment or if the subject no longer meets the study inclusion criteria after enrollment and before the start of treatment, the investigator must have a discussion with the applicant regarding the subject's continuation or withdrawal from the study. The applicant and the investigator need to ensure appropriate record keeping of the decision.

4.4.3 Blinding procedure

Camrelizumab and placebo will be packaged in the same material, with a sealing label affixed to the opening of the box to maintain blinding during the transportation and handover process of the drug. The double-blind technique will be used. The designated study nurse will dispense camrelizumab and the placebo. Drug dispensing will be performed in a separate treatment room whenever possible, and other personnel will not be allowed to enter to prevent breaking the blind. The dispensing nurses will not be involved drug administration during the trial, which will be performed by other study nurses. The subjects, investigators, and the applicant’s staff or their designated personnel participating in the treatment or clinical evaluation of subjects will not be aware of the grouping results.

4.4.4 Unblinding procedure

In this study, the treatment regimen of the subjects will remain blinded to the subjects, investigators, and the applicant’s staff or other designated personnel who participate in the treatment or clinical evaluation of the subjects until the end of the study. During the entire study process, the treatment allocation information is strictly confidential and will not be disclosed until the study database is locked. After the blinded audit indicates that the data quality meets the analysis requirements, the database will be unlocked, the unblinding will be performed, and a blinded audit report will be issued.

Individual unblinding may be performed in accordance with the *CTONG2003-MA-NSCLC-III-009 Emergency Unblinding Procedure* only if the investigator, in the interest of the subject, needs to confirm the subsequent treatment regimen after disease progression. The investigator will perform the first imaging evaluation of the subject’s disease progression according to RECIST v1.1; after confirming the progression 4-6 weeks later, the investigator may unblind the individual after obtaining the approval from the applicant/principal investigator (PI) of the study leader unit. If the clinical condition of the subject is unstable after the first imaging evaluation of the subject’s disease progression, and the investigators determine that they want the subject to receive subsequent treatment as soon as possible, the confirmation at 4-6 weeks is not necessary, and the investigator may unblind the individual after obtaining the approval from the applicant/PI of the study leader unit. If the subject experiences intracranial progression but not systemic progression and is in stable condition, unblinding will not be performed.

If unblinding is needed due to emergency or SAEs, the responsible investigator of the center will apply for unblinding, and the applicant and the PI shall jointly decide whether to unblind.

Before unblinding, the investigators must enter the toxicity level, correlation with the study drugs, and causes of the AEs in the medical records and other documents.

Subjects who are unblinded by the investigator and/or physicians not involved in the study will stop using the study drugs but will continue to be monitored during the trial.

Once unblinding occurs, the circumstances at the time of unblinding (such as the date, reason, and person responsible for unblinding) must be recorded immediately, and the applicant’s clinical research associate (CRA) must be notified as soon as possible. In the event of emergency breaking of blindness, the PI, research center staff and applicant’s staff will be unblinded to provide appropriate follow-up medical care for subjects.

4.5 Dose adjustment and discontinuation

4.5.1 General rules for dose adjustment

1) The reasons, measures and results of dose adjustment or medication delay will be recorded in the subject's medical record and the electronic case report form (CRF).
2) Based on the existing concomitant symptoms at baseline, the investigator will determine whether the dose should be adjusted based on the severity changes in ARs. For example, if a subject's "weak" status is graded as 1 at baseline and as 2 during the study period, the grade of the "weak" status increases by one level, and the dose will be adjusted on the basis of grade 1 toxic reactions.
3) If several ARs of different grades or severities occur simultaneously, the dose adjustment will be based on the ARs with the highest grade.
4) If dose adjustment is needed only because of abnormal hematology values, the dose will be adjusted based on the hematology values before the start of the treatment cycle.
5) If the investigators determine that ARs are unlikely to further develop into serious or life-threatening events, the investigators may continue the current dose without adjustment or suspension of treatment. In addition, dose adjustment or treatment suspension for anemia (nonhemolytic) will not be performed because symptoms can be relieved by blood transfusion.
6) In the judgment of the investigator, if the toxic reaction is caused by one study drug, there is no need to adjust the doses of other drugs.
7) Before disease progression, the permanent discontinuation of one study drug should not affect the continued use of other study drugs.
8) If one study drug is suspended due to related ARs but the other drugs are continued, the treatment is still considered as one complete treatment cycle.

4.5.2 Camrelizumab/placebo dose adjustment

No dose increase or decrease in camrelizumab/placebo will be allowed; the drug can only be suspended or terminated. The maximum suspension interval of camrelizumab/placebo is 9 weeks (calculated from the last actual dosing time); otherwise, camrelizumab is terminated. When camrelizumab/placebo is discontinued for more than 9 weeks, if the investigator determines that the subject can benefit from continued treatment, the investigator will discuss the situation with the drug sponsor.

In addition, when a subject achieves progressive disease (PD) as evaluated by the investigator according to the RECIST 1.1 criteria (unless the subject meets the criteria for continuing treatment after progression), treatment will be permanently discontinued. The subjects are allowed to discontinue treatment due to other events not related to the study treatment, such as medical or surgical procedures or accidents (holidays). The subjects can resume the study treatment within 2 weeks after the interruption of dosing (the planned time of dosing), unless the investigator and the applicant decide otherwise. The reasons for treatment discontinuation must be recorded in the CRF.

4.5.3 Dose adjustment of chemotherapeutic drugs

If the toxic reaction is confirmed to be caused by a specific chemotherapeutic drug, the dose reduction of a single drug is acceptable; if the toxic reaction may be caused by two or more drugs, a dose reduction of all related drugs at the same time can be considered. In cases of drug toxicity, the use of chemotherapeutic drugs can be stopped, and only camrelizumab/placebo is continued, or vice versa. The maximum suspension time of chemotherapeutic drugs is 6 weeks from the last dose of treatment. Before the start of any chemotherapy, supportive treatment for hematological toxicity caused by chemotherapeutic drugs (such as granulocyte-macrophage colony-stimulating factor [GM-CSF]) can be used, but preventive use before the first administration of chemotherapeutic drugs is prohibited.

The CrCl must be ≥ 45 ml/min before the administration of chemotherapeutic drugs. The

maximum interval between the dosing of pemetrexed and/or carboplatin/cisplatin/paclitaxel/albumin-paclitaxel is 6 weeks, allowing the subject's CrCl to return to the required level. If the interval between the two doses is more than 6 weeks, and the CrCl is not restored to ≥45 ml/min, pemetrexed and/or carboplatin/cisplatin/paclitaxel/albumin-paclitaxel must be discontinued.

4.6 Concomitant therapy

4.6.1 Hematologic support

Colony stimulating factors (G-CSF or GM-CSF) or erythropoietin may be used prophylactically during treatment to prevent the occurrence of possible AEs, such as decreased neutrophil count.

4.6.2 Treatment of non-hematologic toxicity

Supportive treatments, such as antiemetics, antibiotics, painkillers, antihypertensive drugs, and blood products, may be used. A rinse can be used for the treatment or prevention of stomatitis.

If the investigators believe that the study endpoints will not be affected, unconventional treatments (such as herbal medicine or acupuncture) and vitamins/minerals can be used. During treatment, patients can receive bisphosphonates for bone metastasis. If painful bone metastases cannot be effectively controlled by systemic treatment or local analgesia, palliative RT can be used on small areas (the RT area must be <5% of the bone marrow area). The clinical comorbidities and AEs will be actively treated. All drugs used in combination will be recorded in the CRF.

4.6.3 Drugs prohibited during the study

Subjects are prohibited from receiving the following treatments during the study period:

- Systemic chemotherapy and biological therapy (including antitumor drugs with immunomodulatory effects, including but not limited to interferons, interleukin-2, thymosin, and immune cell therapy)
- Corticosteroids, other than inhaled steroids for asthma or chronic obstructive pulmonary disease (COPD) as a part of fixed treatment, corticosteroids for the treatment of potential irAEs, physiological doses of corticosteroids, or prophylactic corticosteroids to avoid allergic reactions (e.g., intravenous contrast medium).
- Hepatotoxic drugs

4.7 Drug management

4.7.1 Preservation of drugs

Camrelizumab/placebo should be refrigerated at 2-8 °C, not frozen; protected from light; and kept dry. All trial drugs are shipped to each research center in the cold chain and kept and distributed by designated personnel.

4.7.2 Drug take-back and disposal

In this study, the used and partially used drug containers, vials, infusion bags, and syringes will be destroyed on site according to the applicable guidelines and operating procedures established by the study centers and local institutions.

Unless unused drugs have significant safety issues and require immediate destruction in accordance with local regulations, they will be recalled or destroyed according to the applicable guidelines and operating procedures established by research centers and local institutions.

4.7.3 Study drug records

The designated personnel of the study center will record relevant data, such as the receipt, distribution, use, inventory, destruction, recall, and damage of the study drug, in a timely

manner in accordance with the requirements of relevant laws and guidelines.

5. Clinical evaluation

5.1 Primary study indicators

1) Investigator-assessed systemic PFS: from the time of randomization to the date when the investigators first record tumor progression (assessed according to RECIST v1.1, regardless of whether treatment is continued) or the date of death from any reason, whichever occurs first.
2) Investigator-assessed iPFS: from the time of randomization to the first time the investigator records intracranial tumor progression (assessed according to RECIST v1.1, regardless of whether treatment is continued); the first time that subjects with asymptomatic brain metastases experience one of the symptoms of intracranial hypertension (nausea or vomiting [except when caused by chemotherapy or cerebral infarction], headache, cognitive or emotional disorders, epilepsy, or limb movement disorders); the date of re-exacerbation of intracranial hypertension symptoms in subjects with intracranial hypertension prior to enrollment that is effectively controlled by treatment; or the date of death from any cause, whichever occurs first.

5.2 Secondary study indicators

5.2.1 Efficacy

1) iPFS assessed by the central imaging evaluation team: from the time of randomization to the first time the central imaging evaluation team record intracranial tumor progression (assessed according to RECIST v1.1, regardless of whether treatment is continued); or the date of death from any cause, whichever occurs first.
2) PFS assessed by the central imaging evaluation team: from the time of randomization to the date when the central imaging evaluation team first record tumor progression (assessed according to RECIST v1.1, regardless of whether treatment is continued) or the date of death from any reason, whichever occurs first.
3) iORR: The proportion of subjects with intracranial tumors who achieve complete response (CR) or partial response (PR) according to the RECIST v1.1 criteria. For subjects who do not exhibit disease progression and have not started subsequent antitumor treatment, the best intracranial efficacy will be determined based on the results of all efficacy evaluations.
4) ORR: The proportion of subjects with the best overall efficacy as evaluated as CR or PR according to the RECIST v1.1 criteria. For subjects who do not exhibit disease progression and have not started subsequent antitumor treatment, the best overall efficacy will be determined based on the efficacy evaluation results.
5) OS: The time from the date of randomization to the date of death from any cause. For subjects who are alive at the last follow-up, the OS is censored based on the time of the last follow-up. For subjects lost to follow-up, the OS is censored based on the last confirmed survival time before loss to follow-up.
6) iDOR: The time from the first recorded date of intracranial tumor remission (CR or PR) to the first recorded date of intracranial tumor progressive disease (PD) or death from any cause.
7) DOR: The time from the date of the first recorded tumor remission (CR or PR) to the date of the first recorded PD or death from any cause.

5.2.2 Safety

AEs: All AEs that occur from the first dose to the end of the safety follow-up period will be recorded, and the relationship of the AEs to the study drugs will be determined.

5.2.3 Cognitive function

Changes in neurocognitive function before and after treatment with camrelizumab/placebo

combined with chemoradiotherapy will be evaluated with the MMSE and HVLT-R.

5.3 Exploratory study indicators

5.3.1 Patient-reported outcomes

The EORTC QLQ-C30 is used to assess the QoL of cancer patients and contains 30 items divided into 15 domains, with five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and 6 single items (difficulty breathing, sleeping disorders, decreased appetite, constipation, diarrhea, and economic impact). A 7-point scale is used for overall health status/QoL (1=very poor, 7=excellent); other items are scored on a 4-point scale (1=none, 2=somewhat, 3=more, 4=a lot).

The EORTC QLQ-BN20 is a supplementary questionnaire for assessing the quality of life in patients with brain tumors, used in conjunction with the EORTC QLQ-C30. The QLQ-BN20 includes four multi-item scales that assess future uncertainty, visual impairment, motor dysfunction, and communication deficits. Additionally, it contains seven single-item scales that evaluate symptoms such as headache, seizures, drowsiness, hair loss, itchy skin, leg weakness, and bladder control. Items on the questionnaire are rated on a 4-point scale (1 = Not at all, 2 = A little, 3 = Quite a bit, 4 = Very much).

Assessment of quality of life: The subjects' quality of life is assessed and recorded using the EORTC QLQ-C30 and EORTC QLQ-BN20 questionnaires. It is recommended that participants complete the quality-of-life assessments prior to drug administration and adverse event evaluation. The questionnaires should be completed in the following order: first the EORTC QLQ-C30, followed by the EORTC QLQ-BN20.

5.4 Imaging scan sites

The method used for tumor imaging evaluation at baseline and at each subsequent follow-up evaluation will be consistent; CT or MRI is recommended. Other involved sites will be examined as indicated by each subject’s signs and symptoms. Baseline tests of the chest, upper abdomen, brain and all known or suspected disease sites will be performed. Each subsequent clinical tumor imaging evaluation will include the chest, brain, and upper abdomen. Researchers may increase the frequency of imaging examinations according to the patient’s condition.

5.5 Assessment time points

The baseline tumor assessment will be performed within 28 days before the first dose. Imaging data obtained before providing informed consent can be used in tumor assessment during the screening period as long as the protocol requirements are met. During the study, imaging assessments will be performed every 6 weeks (±7 days) after the first drug treatment until imaging PD is recorded. For the subjects whose first recorded remission (CR or PR) or PD could not be confirmed by initial imaging scans, it is recommended to reconfirm remission and PD after no less than 4 weeks.

The criteria for PD are as follows:

1) At 2 consecutive visits, the sum of the diameters of the target lesions is increased by ≥20% compared with the minimum value (the smallest sum of diameters, which may occur at the baseline or in the subsequent visits), and an increase is at least 5 mm, and/or
2) At the time of PD confirmation, the nontarget lesions or new lesions have significantly progressed compared with those at the first time point when the progression of the nontarget lesions or the new lesions is discovered (aggravation to the extent that even if the target lesions show CR, PR, or SD, the total progression of the lesions has increased enough to stop treatment), and/or
3) Compared with the first scan when new lesions are discovered, other new lesions appear at the PD confirmation scan. If PD is not confirmed, the patient will continue to receive

the study drug, and imaging evaluation will be performed until PD is confirmed.

Treatment will be terminated for subjects with PD. For patients whose treatment is discontinued for reasons other than PD found by imaging, imaging assessment will be performed according to the image assessment cutoff point until any of the following events occur: start of new antitumor treatment, PD, withdrawal of informed consent by the subject and death.

For subjects who are found to be clinically unstable, the treatment will be discontinued after the first appearance of investigator-evaluated PD by imaging is confirmed by the center, and there is no need to repeat the imaging examination to confirm PD.

Clinical stability is defined as follows:

- The absence of clinically significant symptoms and signs (including deterioration of laboratory test values) suggesting disease progression
- No decrease in ECOG score
- No rapid disease progression
- No progressive tumor in important anatomical locations that require emergency medical intervention (such as spinal cord compression).

If the investigator is unable to ascertain PD, especially PD of nontarget lesions and new lesions, the subjects will continue to receive treatment, and the subject's disease status will be reevaluated at the time of clinical indication or at the next scheduled evaluation. If PD is confirmed by reexaminations, the date of progression will be recorded as the date of initial discovery.

The suspension of one or more study drugs does not affect the assessment frequency using RECIST 1.1.

6. Safety evaluation

6.1 Safety parameters

The safety parameters include AEs related to the study treatment, SAEs, abnormal laboratory test results, clinical manifestation characteristics, severity, time of occurrence, duration, treatment methods, and prognosis of unexpected safety events.

6.2 Abnormal laboratory test results

Laboratory examination: blood/urine/other samples will be collected according to the study procedure table, and testing will be completed in our laboratory.

Abnormal results of the following laboratory examinations should be recorded on the corresponding CRF nonserious AE page or the SAE report form (written CRF or electronic CRF):

- All laboratory test results that are clinically significant or meet the definition of an SAE
- All abnormal laboratory test results that require subjects to suspend or discontinue the use of the study drugs
- All abnormal laboratory test results that require the subjects to receive specific symptomatic treatments.

It is preferable for the reporting investigator to use clinical terminology rather than laboratory test terminology whenever possible (e.g., anemia rather than low hemoglobin).

6.3 Safety evaluation criteria

The evaluation of AEs includes type, incidence, severity (graded according to NCI CTCAE 5.0), occurrence and end time, correlation with study treatment, and outcome.

7. Adverse events

7.1 AEs

Definition of AE: An AE is any adverse medical event that occurs in a subject in a clinical trial after receiving a drug but does not necessarily have a causal relationship with the treatment.

An AE can be any unfavorable unexpected symptoms, signs, abnormal laboratory test results or diseases and is included but not limited to the following conditions:

1) Pre-existing (prior to the enrollment of clinical trials) medical conditions/diseases are recorded as AEs only if the condition worsens (including worsening of signs, symptoms, abnormal laboratory test results) after initiation of the study drug.

2) New AEs are any new adverse medical conditions (including symptoms, signs, and newly diagnosed diseases).

3) Abnormal laboratory test results with clinical significance.

Diagnostic or therapeutic invasive (such as surgery) and noninvasive procedures should not be reported as AEs; however, these procedures should be reported as AEs when the disease condition that leads to the procedure meets the definition of an AE. For example, acute appendicitis that occurs during the reporting period of an AE should be reported as an AE, and the appendectomy should be recorded as the treatment of this AE.

Researchers will record the details of any AEs that occur, including the name of the AE, occurrence and end time, severity (grading in accordance with NCI CTCAE v5.0), correlation between the AE and study drugs, duration, measures taken for study drugs due to the AE, the outcome of the AE, and whether it is a SAE, in the CRF.

7.2 Criteria for determining AE severity

The grading criteria of NCI-CTCAE <5.0> will be used to determine the severity of AEs, and the following criteria will be used if any AEs that are not listed in the NCI-CTCAE <5.0> occur:

Grade I: mild with no clinical symptoms or mild clinical symptoms; only clinical or laboratory test results are abnormal; no treatment is needed.

Grade II: moderate, with only minor, local, or noninvasive treatment needed; age-matched activities of daily living (ADLs), such as cooking, shopping, making phone calls, and counting money, are limited.

Grade III: severe condition or medically serious symptoms but not currently life-threatening; leading to hospitalization or prolongation of hospitalization, disability, or limitations in self-care ADLs, such as bathing, dressing, undressing, eating, going to the bathroom, taking medication, etc.

Grade IV: Life-threatening; emergency treatment is needed.

Grade V: Death due to AE.

7.3 SAEs

1) An SAE is defined as an AE that occurs during a clinical trial that meets one or more of the following criteria:

- Event that led to death
- Life-threatening (referring to the risk of the subject's death at the time of the event/response, not the assumption that exacerbation of the condition may lead to death)
- The need for hospitalization or prolonged hospitalization
- Event that led to permanent or severe disability/loss of function
- Congenital anomalies or birth defects
- Other important medical events (events/reactions that are not immediately life-threatening and do not lead to death or hospitalization but, according to reasonable medical and scientific judgment, may cause harm to the subject or may require intervention [such as drugs or surgery] to prevent the serious consequences listed in the above definition).

2) Hospitalization

AEs in clinical trials that lead to hospitalization (even if less than 24 hours) or prolonged hospitalization should be considered SAEs, except in the following situations:

- Rehabilitation institution

- Nursing home
- Routine emergency room visit (less than 24 hours)
- Same-day surgeries (e.g., outpatient/same-day/ambulatory surgeries)
- Social reasons (medical insurance reimbursement, etc.)
- Hospitalization or prolonged hospitalization that is not related to an AE, including but not limited to the following situations:
    - Hospitalization for treatment due to an underlying disease, and hospitalization is not related to new AEs or the exacerbation of the original disease (such as persistent abnormal laboratory test results before the diagnostic test)
    - Hospitalization for management reasons (e.g., annual routine physical examination)
    - Hospitalization as stipulated in the trial protocol during the clinical trial (e.g., operation in accordance with the requirements of the trial protocol)
    - Elective hospitalization unrelated to the AE (e.g., elective cosmetic surgery)
    - Previously scheduled pretreatments or surgical procedures (should be recorded in the entire trial protocol and/or the baseline data of the individual subjects)
    - Hospitalization due to the use of blood products.

3) Other antitumor therapies

If a subject begins other new antitumor treatments before the end of the safety follow-up period, the collection of non-death AEs/SAEs that are suspected to be unrelated to the study drugs ends when the new antitumor treatments start. If death occurs during the safety follow-up period, it is reported as an SAE regardless of whether the subject receives other treatments.

4) Overdose

Drug overdose refers to an overdose of the study drug by the subject within 24 hours (the specific time is adjusted according to the specific regimen) at a dose higher than the dose prescribed by the investigator's medical order. Drug overdose combined with an SAE should be reported to the study drug manufacturer as an SAE.

7.4 Definition of unexpected safety events

Expected AEs are AEs that commonly occur in completed/ongoing studies. These AEs should be collected systematically (via the grading system) and standardized, and methods for determining expected AEs should be described. This type of AE has been observed in previous studies and is not predicted based on the chemical properties of the drug itself.

An unexpected safety event is an event or result that meets the following criteria:

The post-marketing instructions for the study drugs are used for the prospective assessment of AEs. If the nature, severity, specificity, and results of an event are inconsistent with the description in the post-marketing instructions, then the event is considered an unexpected event.

7.5 AE/SAE collection and follow-up visits

AE information should be collected from the first treatment to the end of the safety follow-up period, that is, 90 days after the last use of camrelizumab/placebo.

If the subjects start using new antitumor treatments before the end of the safety follow-up period, the collection of non-death AEs/SAEs that are suspected to be unrelated to the study drugs ends at the start of the new antitumor treatment.

If death occurs during the safety follow-up period, it is reported as an SAE regardless of whether the subject receives other treatments. After the safety follow-up period, the investigators report only SAEs related to the study drug to the drug safety department of the manufacturer.

All AEs/SAEs will be followed up until the resolution of symptoms, a return of the clinically relevant changes in laboratory tests to baseline and/or ≤ Grade 1, a reasonable explanation (such as loss to follow-up or death), or the event is conclusively determined to be unrelated to the study drug or study procedure by the end of the safety follow-up period.

At each visit, the investigators will ask about AEs/SAEs that occurred since the previous visit and provide follow-up information in a timely manner according to the responses.

7.6 Determination of the relationships between AEs and study drugs

The investigators will use a comprehensive assessment to determine whether there is a reasonable possibility that the study drug could cause or contribute to the AEs. The determining factors include whether the AEs occurred in a reasonable chronological order with the dosing of the study drug, characteristics of the study drug, toxicology and pharmacology of the study drug, treatment effects, combined medication use, underlying diseases, medical history, family history, and dechallenge and rechallenge responses of the subjects. The possible relationships between AEs and the study drugs will be classified according to the five levels of "definitely related, possibly related, possibly irrelevant, definitely irrelevant, and unable to determine".

7.7 SAE reporting procedure

In the event of an SAE, whether reported for the first time or at follow-up, the investigator must immediately complete the *Serious Adverse Event Report Form*, sign and date it, and report the event to the appropriate authorities within 24 hours of the investigator being notified. If the SAE occurs after initiation of camrelizumab/placebo, the event must be reported to the drug safety department of the study drug manufacturer.

All SAEs will be recorded in detail, including symptoms, severity (refer to the NCI-CTC 5.0 grading), correlation with each study drug, time of occurrence, treatment time, measures taken for each study drug due to the SAE, time and methods of follow-up, and outcomes. If the investigator believes that an SAE is not related to the study drug but is potentially related to the study conditions (such as termination of the original treatment or comorbidities during the trial), this relationship should be described in detail in the narrative section of the SAE report form. If the severity of an ongoing SAE or its relationship with the study drugs changes, a follow-up report will be submitted immediately. If the investigator believes that previously reported SAEs are misreported, the investigator can correct, withdraw or downgrade the cases in a follow-up report and report the cases according to SAE reporting procedures.

7.8 Pregnancy reporting procedure

If a female subject becomes pregnant during the study, the subject should immediately stop using the study drug and withdraw from the study. If the female partner of a male subject becomes pregnant during the study, the subject may continue the study.

During the clinical study, the investigators must fill out the *Clinical Trial Pregnancy Report/Follow-up Form* within 24 hours of learning about the pregnancy and report it to the relevant departments. If the pregnancy occurs after the initiation of camrelizumab/placebo, a *Clinical Trial Pregnancy Report/Follow-Up Form* must be completed and reported to the drug safety department of the study drug manufacturer within 15 days of the investigator being notified of the pregnancy.

The investigators will follow a pregnancy to the final result (including early termination of pregnancy or delivery), follow the mothers for 1 month after delivery, and report the results to the relevant departments and the drug safety department of the study drug manufacturer.

If the pregnancy results in an ectopic pregnancy, spontaneous abortion, intrauterine fetal death, neonatal death, or congenital anomalies, it is considered an SAE and is reported according to the time requirements of the SAE.

If an SAE occurs while the subject is pregnant, the *Serious Adverse Event Reporting Form* must be completed, and the SAE reporting procedure must be followed.

7.9 Disease progression and death reporting

Disease progression is defined as deterioration of the subject's condition caused by the indications of the study. Progression includes imaging evidence and clinical symptoms and

signs. New metastatic lesions of the primary tumor or progression of the original metastatic lesions are considered disease progression.

Life-threatening events that require hospitalization or prolonged hospitalization and events that lead to permanent or severe disability/loss of function due to symptoms and signs of disease progression are not reported as SAEs. If there is any uncertainty about whether an SAE is due to disease progression, it should be reported as an SAE.

In the study population of this trial, "disease progression" is an expected condition and should not be reported as an AE. When disease progression occurs, the events used to confirm disease progression should be reported as AEs. For example, if a subject develops epilepsy that is determined to be related to brain metastases, the AE should be recorded as "epilepsy" rather than "disease progression" or "brain metastases".

During the safety follow-up period, a death that is possibly caused by the symptoms and signs of disease progression according to the investigator's evaluation should be reported as an SAE.

However, the word "death" should not be used as the term for an AE or SAE but rather as the result of the event, and the event causing or leading to death should be recorded as an SAE. If the cause of death cannot be determined at the time of reporting, it is recorded as "death from unknown causes".

7.10 Abnormal liver function test results

If an abnormal AST and/or ALT level occurs in combination with an abnormally high total bilirubin (TBIL) level, all three of the following conditions are met, and there is no other cause of the abnormality, the SAE reporting process should be followed.

Conditions	Judgment criteria
(1) Abnormal ALT or AST	Normal baseline: ALT or AST> 3 × ULN during the treatment period Abnormal baseline: treatment-period ALT or AST > 2 × baseline level and ALT or AST level > 3 × ULN; or ALT or AST level > 8 ×ULN.
(2) Abnormal TBIL	Normal baseline: TBIL> 2 × ULN during the treatment period Abnormal baseline: increase of TBIL during the treatment period is > 1 × ULN or TBIL level is > 3 × ULN.
(3) No hemolysis and alkaline phosphatase < 2 ×ULN (or no information obtained)	

ULN (upper limit of normal)

If abnormal AST and/or ALT levels combined with abnormally increased TBIL levels are detected during the safety follow-up period, it is recommended that the subject return to the study center for evaluation and confirmation as soon as possible (preferably within 48 hours) after learning the abnormal results.

8. Independent imaging evaluation

The imaging evaluation in this trial will be performed at each study center (on site review), and the central imaging evaluation team will perform independent imaging evaluations (central review) of the efficacy endpoints.

The imaging evaluation at the research centers will be performed by an experienced and qualified research physician designated by each center. Each research center will record all the imaging examination data related to the efficacy evaluation onto CD-ROMs for archiving and regularly send them to the central imaging evaluation team for evaluation.

Independent imaging evaluations will be performed by 2 independent radiologists in a blinded manner. If the evaluation results of the two independent radiologists are inconsistent, a third radiologist will make the final decision. For details, please see the independent image

evaluation handbook.

Each study center and the independent radiologists will conduct efficacy evaluations via tumor imaging according to RECIST 1.1 standards.

9. Statistical analysis

See the Statistical Analysis Plan（SAP） for details.

10. Ethical considerations

10.1 Ethical norms

The study will be performed in strict compliance with the ethical guidelines for human medical research of the *Declaration of Helsinki* and relevant Chinese clinical trial regulations. The investigators will be responsible for providing the clinical trial protocols, informed consent forms, and information provided to the subjects to the ethics committee to obtain independent approval documents for the implementation of the clinical study.

Approval documents from the ethics committee must be obtained before the start of the study.

Neither the study applicant nor the investigator will unilaterally modify the trial protocol of the study without the other's consent.

During the clinical study, any issue related to the safety of clinical study must be reported to the ethics committee in a timely manner. The end or early termination of the clinical study must also be reported to the ethics committee.

The personnel involved in the implementation of this study must have corresponding qualifications, and their educational background, training experience, and experience in carrying out their respective jobs must all meet the requirements.

10.2 Informed consent

10.2.1 Informed consent form and other written information for subjects

The informed consent form will describe the study medications and study processes in detail and fully explain the study risks to the subjects. Before administering the study drug, written informed consent must be obtained.

10.2.2 Informed consent process and records

Informed consent starts before the individual agrees to participate in the clinical study and continues during the entire clinical study process. The risks and possible benefits of participating in the study will be discussed in detail with the subjects and their families. The investigator will explain the clinical study to the subjects and answer any questions the subjects may have. The subjects can only participate in the study after signing the informed consent form. During the clinical study process, subjects can withdraw their consent at any time.

10.3 Confidentiality of subject information

The confidentiality of subject information is strictly implemented by the investigators, the participating researchers, the applicant, and the agents.

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