Supplementary Appendix

Supplementary Method

CD19 CAR construct and CAR T-cell manufacture

Humanized CD19 CARs were lentiviral vectors carrying a second-generation CAR with 41-BB co-stimulatory and CD3ζ signaling domains (from Shanghai YaKe Biotechnology Ltd., Shanghai, China). The antigen recognition domains of CD19-specific CARs are single-chain variable fragments obtained from a human antibody phage display library. Autologous peripheral blood mononuclear cells (PBMCs) were collected from patients through leukapheresis. PBMCs were stimulated with magnetic beads coated with anti- CD3/CD28 antibodies (Thermo Fisher Scientific) overnight. The next day, transduction via a lentiviral vector was performed at a multiplicity of infection 1:8 ratio. Transduced cells were cultured in X-VIVO 15, a serum- free medium (Lonza) with 300 IU/mL interleukin- 2, for the duration of cell culture (7-11 days).

Supplementary Table

Table S1. Adverse events during ZR2 regimen

Adverse events	Any Grade (n=43)	Grade 3 or Higher (n=43)
Hematological toxicities		
Neutrophil count decreased	35 (81.4%)	13 (30.2%)
White blood cell decreased	24 (55.8%)	4 (9.3%)
Lymphocyte count decreased	20 (46.5%)	9 (20.9%)
Anemia	18 (41.9%)	2 (4.7%)
Platelet count decreased	6 (14.0%)	1 (2.3%)
Laboratory values		
Hypoalbuminemia	32 (74.4%)	0
Hypokalemia	25 (58.1%)	4 (9.3%)
Hypophosphatemia	16 (37.2%)	0
Hypocalcemia	14 (32.6%)	1 (2.3%)
Creatinine increased	11 (25.6%)	0
Fibrinogen decreased	6 (14.0%)	0
INR increased	3 (7.0%)	0
Blood bilirubin increased	2 (4.7%)	0
Aspartate aminotransferase increased	1 (2.3%)	1 (2.3%)
Alanine aminotransferase increased	1 (2.3%)	1 (2.3%)
Activated partial thromboplastin time prolonged	1 (2.3%)	0
Respiratory diseases		
Dyspnea	4 (9.3%)	0
Cough	2 (4.7%)	0
Lung infection	2 (4.7%)	1 (2.3%)
Laryngeal hemorrhage	1 (2.3%)	0
Pharyngolarygeal pain	1 (2.3%)	0
Gastrointestinal disorders		
Abdominal pain	4 (9.3%)	0
Nausea	3 (7.0%)	0
Heart disease		
Ventricular tachycardia	2 (4.7%)	0
Sinus bradycardia	1 (2.3%)	0
General conditions		
Fever	8 (18.6%)	0
Fatigue	3 (7.0%)	0
Dizziness	2 (4.7%)	0
Weight loss	1 (2.3%)	0
Others		
Rash	10 (23.3%)	3 (7.0%)

Pruritus	6 (14.0%)	2 (4.7%)
Edema limbs	3 (7.0%)	0
Peripheral sensory neuropathy	3 (7.0%)	0
Flank pain	2 (4.7%)	0
Pain	2 (4.7%)	0
Wound infection	1 (2.3%)	1 (2.3%)
Non-cardiac chest pain	1 (2.3%)	0
Thromboembolic event	1 (2.3%)	0

Efficacy and safety of CD19 CAR-T cells in the treatment of newly diagnosed large B-cell lymphoma

Clinical study protocol

Scheme version No.: V1.5

Scheme version date: November 20, 2023

Clinical Research Unit: The First Affiliated Hospital of Zhejiang University School of Medicine

Initiator: Professor Huang He

Programme revision history

Version	**Date**	**Release Notes**
V1.0	2020-9-22	First draft
V1.1	2020-10-29	Revised version
V1.2	2023-6-7	Revised version
V1.3	2023-07-12	Revised version
V1.4	2023-11-13	Revised version
V1.5	2023-11-20	Revised version

Investigator's statement and signature page

This study is a prospective clinical study, and the methodology, equipment and drugs used in the study have been widely used in clinical practice. In this study, a strict adverse event monitoring system will be established, and all adverse events will be carefully recorded and dealt with in a timely and effective manner. If any serious adverse event or important adverse event occurs, whether it is related to the study intervention or not, and whether the intervention has been carried out or not, the sponsor of the study must be notified in time, and whether to stop the study must be decided in time according to the situation. The investigator guarantees that the personal data of the subject will be kept strictly confidential: all subject information and images will be identified by numbers rather than names; identifiable information will not be disclosed to members outside the study team unless permission is obtained from the subject; all study members and study sponsors are required to abide by the principle of confidentiality; All study files will be kept in a locked filing cabinet for the study personnel's reference only; during and after the study, members of the government administration or the ethics committee will be allowed to conduct spot checks and supervision on the personal data of the subjects as required; No personal information will be disclosed when the results of this study are published.

Signature of investigator

I have read and agreed to the protocol proposed in this document, and agreed to the relevant contents of the protocol. During the trial, I will strictly abide by the laws and regulations of the People's Republic of China and relevant rules and regulations, perform the duties of the researcher and abide by the confidentiality provisions.

Research setting: The First Affiliated Hospital of Zhejiang University School of Medicine

Name of researcher: He Huang

Investigator Title: Principal Investigator

Signature of investigator:

Date of signature:

Summary of the programme

Study name	Efficacy and safety of CD19 CAR-T cells in the treatment of newly diagnosed large B-cell lymphoma
Research phase	Phase II study
Study design	Single-arm, open-label, single-center design
Number of research centers	1
Sample size	40 cases
Indications	High-risk diffuse large B-cell lymphoma, high-grade B-cell lymphoma
Purpose of the study	Main purpose: To evaluate the efficacy of CD19 CAR-T in newly diagnosed large B-cell lymphoma. Secondary Purpose: To assess the safety of CD19 CAR-T in newly diagnosed large B-cell lymphoma. Exploratory Purpose: CD19 CAR-T expansion in vivo, persistence, and its ability to deplete B cells in vivo.
Primary endpoint	Complete response rates after CD19 CAR-T cell therapy
Secondary endpoint	1） Overall response rate (ORR = CR + PR) according to Lugano 2014 criteria; 2） Duration of remission (DOR); 3） PFS and OS; 4） Safety 5） Characteristics of relapse (including expression of CD19 and CD20) 6） Exploratory study endpoints: The expansion and persistence of CAR-T cells in vivo and the clearance of B cells.
Inclusion criteria	1） Age ≥ 18 years old, regardless of gender; 2） According to the 2016 edition of WHO classification of lymphocytic neoplasms, the histological diagnosis included high-grade B-cell lymphoma (including high-grade B-cell lymphoma NOS, high-grade B-cell lymphoma with C-MYC, BCL-2 and/or BCL-6 rearrangement), diffuse large B-cell lymphoma NOS and IPI score ≥ 3 at diagnosis; 3） Lymphoma cells expressed CD19 and CD20 positively. 4） Serum total bilirubin ≤ 51 mol/L, serum ALT and AST ≤ 3 times of the upper limit of normal range, serum creatinine ≤ 176.8μmol/L; 5） Echocardiography showed left ventricular ejection fraction (LVEF) ≥ 50%; 6） The subject had no active pulmonary infection, and the oxygen saturation of inspired air was ≥ 92%. 7） The estimated survival time is more than 3 months; 8） ECOG score 0-2;

	9） The subjects participated in the trial voluntarily and signed the informed consent form.
Exclusion criteria	Subjects who met any of the following exclusion criteria were excluded from the study: 1） Patients with central involvement, history of epilepsy or other central nervous system diseases; 2） Patients with previous QT prolongation or severe heart disease; 3） Pregnant or lactating women (the safety of this treatment for unborn children is unknown); 4） Uncured patients with active infection; 5） Active hepatitis B or hepatitis C virus infection; 6） Previous use of any gene therapy product; 7） Insufficient amplification (< 5-fold) in response to CD3/CD28 costimulatory signals; 8） Creatinine > 2.5 mg/DL or ALT/AST > 3 times normal or bilirubin > 2.0 mg/DL; 9） Those who suffer from other uncontrolled diseases and are not considered suitable for enrollment by the investigator; 10） People living with HIV; 11） Any condition which, in the opinion of the investigator, may increase the risk to the subject or interfere with the outcome of the trial.
Study termination criteria	1） The enrollment, treatment and follow-up of the clinical study were successfully completed and reached the target number of cases. 2） The efficacy of clinical trials far exceeded expectations. 3） Serious uncontrollable adverse events occurred in clinical trials.
Visit plan	1） Screening period and baseline check; 2） Bridging treatment period (two cycles of ZR^2); 3） Cell preparation and lymphodepletion period; 4） CAR-T cells were reinfused on day 0; 5） Return visit shall be carried out on the 4th, 7th, 9th, 11th, 14th, 21st and 30th day after infusion (monitor the patient's condition-collect blood samples to judge the CAR-T cell expansion status, blood routine, blood biochemistry and other indicators of the subject after infusion; and tissue samples, cerebrospinal fluid, pleural effusion and other indicators may need to be collected according to the change of the subject's condition; D30 efficacy evaluation); 6） The follow-up period of CAR-T therapy was 60 days (D31-90), and the evaluation was conducted once a month, and the efficacy was evaluated on D90. 7） Subjects were evaluated every 3 months within 3-24 months after infusion; 8） Subjects were evaluated every 6 months for 2-5 years after infusion.
Test process	**1. Sign the informed consent** An Informed Consent Form, signed and dated by the subject and reviewed by the Ethics Committee, must be obtained prior to any investigational procedure or evaluation.

	II. Screening period inspection Screening examinations included medical history, physical examination, vital signs, laboratory tests and imaging examinations. **III. Bridging Scheme** Before CAR-T cell infusion, the patients were treated with " Zanubrutinib + Lenalidomide + CD20 monoclonal antibody" for 2 cycles. **IV. Evaluation before CAR-T cell therapy** After the completion of 2 cycles of bridging therapy, the efficacy was evaluated by PET-CT, and the patients with CR, PR or SD efficacy evaluation compared with the baseline were enrolled in CAR-T cell therapy, and the patients with PD efficacy evaluation were excluded from the group and did not receive CAR-T cell therapy. **5. Apheresis and lymphodepletion** In the apheresis stage, lymphocyte collection was completed and CAR-T cell preparation was prepared. On days -4 to -2 prior to cell infusion (day 0), subjects were pretreated with "Fludarabine + Cyclophosphamide" (FC regimen) as follows: Fludarabine: 30 $mg/m^2/d$, intravenous infusion, once a day, from -4 to -2 days, for three consecutive days; Cyclophosphamide: 500 $mg/m^2/d$, intravenous infusion, once a day, from -3 days to -2 days, for two consecutive days. Treatment begins with an intravenous infusion of cyclophosphamide within 30 minutes, followed by an intravenous infusion of fludarabine. **VI. CAR-T cell therapy and observation** The drug was administered by intravenous infusion at one time. The infusion time was within 30 minutes. **VII. Follow-up** Follow up according to the time points specified in the protocol, and complete the evaluation of test items, effectiveness and safety.
Statistical analysis	See the scheme for the sample size estimation method; Safety data included adverse events observed during the trial and changes in laboratory data before and after treatment. Adverse events Statistical descriptions were used to calculate the incidence of each adverse event and the overall incidence of adverse events.
Quality Management	Conduct research, generate, record and report data in strict accordance with the Quality Management Standards for Clinical Research of Cellular Immunotherapy and the corresponding regulatory requirements.

Catalog

Catalog

1. Research Background

1.1. Large B-Cell Lymphoma

Large B cell lymphoma (LBCL) is the most common lymphoid malignancy, accounting for 25-35% of newly diagnosed non-Hodgkin lymphomas. Currently, immunochemotherapy regimens such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) remain the standard first-line treatment for LBCL, resulting in durable remissions in approximately 60% of patients.(1-3) However, outcomes were significantly worse in the high-risk LBCL subgroup, including patients with a high International Prognostic Index (IPI) score (IPI $\geqslant$ 3) and patients with High grade B cell lymphoma (HGBL). For these high-risk patients, the complete response (CR) rate of the standard R-CHOP regimen is less than 50%, and the progression-free survival (PFS) and overall survival (OS) were significantly lower than those in the low-risk cohort(4, 5). Given this poor prognosis, patients with high-risk LBCL need more effective first-line treatment options early in the course of the disease.

1.2. Chimeric Antigen Receptor T Cell

Chimeric antigen receptor (CAR) modified T cells (CAR-T) is a kind of adoptive cellular immunotherapy developed rapidly in recent year(6). The structure of CAR generally consists of four parts: ① antigen-binding domain, usually derived from single-chain variable fragments of antibodies, which can specifically recognize and bind tumor-associated antigens; ② The hinge region is used to connect the single-chain antibody and the transmembrane region. The length of this region may greatly change the strength of the transmitted signal, thereby affecting the function of CAR-T cells (7, 8). ③a transmembrane region for anchoring the CAR to the cell membrane and mediating signal transmission; ④ Intracellular signal transduction domain, the cascade structure of costimulatory receptor intracellular domain and CD3 ζ transmit activation signals to CAR-T cells. By means of gene engineering technology, the said four parts are serially connected, fused and expressed on T cell membrane, so as to endow T cell with targeting, killing activity of specific tumor tissue and lasting amplification capacity of T cell itself (6, 7, 9).

1.3. Advances in CAR-T Cell Therapy for Large B-Cell Lymphoma

At present, the safety and efficacy of CD19 CAR-T cell therapy have been widely verified in clinical trials of international centers, and the clinical management scheme of CAR-T therapy in our center has been very mature. Data from major centers around the world on CAR-T cell therapy for relapsed and refractory LBCL show that the complete response rate is still low, and the efficacy needs to be improved.(10, 11). At present, patients with relapsed and refractory CAR-T cell therapy usually have undergone multi-line chemotherapy, which can impair T cell function, weaken the expansion and persistence of CAR-T cells, and affect the efficacy of CAR-T cells. Therefore, the front-line therapy of CAR-T cells is one of the potential directions to improve the efficacy of CAR-T. However, there is still a lack of data on the first-line CAR-T cell therapy for LBCL, and how to optimize the complete regimen of CAR-T first-line therapy to improve the efficacy and safety needs to be explored. At present, some targeted drugs such as BTK inhibitors and lenalidomide have shown certain efficacy and good safety in the treatment of LBCL.(12, 13) The combination

of targeted drugs also showed good efficacy in refractory and relapsed LBCL(14). Therefore, the combination of targeted drugs as bridging therapy may be effective in reducing the tumor burden of newly diagnosed LBCL before first-line CAR-T therapy and is well tolerated. Therefore, we believe that targeted therapy combined with sequential CAR-T cell therapy has a good clinical prospect as a first-line treatment strategy for high-risk LBCL. This comprehensive strategy not only circumvents the impairment of CAR-T efficacy by chemotherapy, but also enhances the therapeutic effect through non-cytotoxic mechanisms. More importantly, for some patients with initial intolerance to chemotherapy, new treatment options are urgently needed to reduce the use of chemotherapy drugs and achieve "chemo-free". To sum up, our center intends to apply for the clinical trial of CD19 CAR-T cells in the treatment of newly diagnosed high-risk LBCL.

2. Purpose of the Clinical Study

1) To evaluate the effectiveness of CD19 CAR-T in newly diagnosed high-risk LBCL.
2) To evaluate the safety and feasibility of CD19 CAR-T in newly diagnosed high-risk LBCL.

3. Overall Design

3.1 Research Methods

This study used a prospective, open-label, single-center study design. The purpose of this study was to evaluate the efficacy and safety of CD19-targeted CAR-T cells in the treatment of newly diagnosed high-risk LBCL.

3.2 Subject Selection

3.2.1 Subject Inclusion Criteria

1) Age ⩾ 18 years old, regardless of gender;
2) According to the 2016 edition of WHO classification of lymphocytic neoplasms, the histological diagnosis included high-grade B-cell lymphoma (including high-grade B-cell lymphoma NOS, high-grade B-cell lymphoma with C-MYC, BCL-2 and/or BCL-6 rearrangement), diffuse large B-cell lymphoma NOS and IPI score ⩾ 3 at diagnosis;
3) Lymphoma cells expressed CD19 and CD20 positively.
4) Serum total bilirubin ⩽ 51 mol/L, serum ALT and AST ⩽ 3 times of the upper limit of normal range, serum creatinine ⩽ 176.8μmol/L;
5) Echocardiography showed left ventricular ejection fraction (LVEF) ⩾ 50%;
6) The subject had no active pulmonary infection, and the oxygen saturation of inspired air was ⩾ 92%.
7) The estimated survival time is more than 3 months;
8) ECOG score 0-2;
9) The subjects participated in the trial voluntarily and signed the informed consent form.

3.2.2 Subject Exclusion Criteria

Subjects who met any of the following exclusion criteria were excluded from the study:

1) Patients with central involvement, history of epilepsy or other central nervous system diseases;
2) Patients with previous QT prolongation or severe heart disease;

3) Pregnant or lactating women (the safety of this treatment for unborn children is unknown);
4) Uncured patients with active infection;
5) Active hepatitis B or hepatitis C virus infection;
6) Previous use of any gene therapy product;
7) Insufficient amplification (< 5-fold) in response to CD3/CD28 costimulatory signals;
8) Creatinine > 2.5 mg/DL or ALT/AST > 3 times normal or bilirubin > 2.0 mg/DL;
9) Those who suffer from other uncontrolled diseases and are not considered suitable for enrollment by the investigator;
10) People living with HIV;
11) Any condition which, in the opinion of the investigator, may increase the risk to the subject or interfere with the outcome of the trial.

3.2.3 Criteria and Procedures for Discontinuation of Study by Subjects

1) Subjects who did not complete the study protocol were considered to have prematurely terminated the study. The reason for the termination (e.g., voluntary withdrawal, serious adverse reaction, death) must be recorded on the Case Report Form (CRF) and retained for the time period required by the GCP. Possible reasons for early termination and withdrawal include:

A. Adverse events. The subject has an adverse event, and the investigator believes that the discontinuation of the trial is based on the medical decision to maximize the benefit of the subject;

B. Lack of efficacy. The investigator determined that the subject did not benefit from the trial treatment and that continued participation in the study may place the subject at an unpredictable risk;

C. Significant programme violations. After CAR-T cell infusion, it is found that the subject does not meet the entry and exclusion criteria, or does not comply with the requirements of the protocol;

D. The subject refuses to continue the treatment or observation and voluntarily withdraws;

E. Subjects lost to follow-up. The subject did not return to the hospital on time for follow-up, and the investigator failed to contact the subject. Efforts to contact the subject must be documented;

F. Death of the subject. Record and report according to SAE;

G. Pregnancy events. Once a subject is found to be pregnant, the subject must be immediately withdrawn from the study and documented and reported as an SAE;

H. Study Termination. Termination of the Study is requested by the Partner, the IRB, the IEC or the Regulatory Authority;

I. Subjects who may not be able to complete the study for other reasons or who are not suitable for participation in the investigator's judgment.

2) Operation/procedure for study withdraw

In order to ensure the maximum rights and interests of the subjects, the investigator may suspend the subjects who are not suitable for the study protocol according to the clinical diagnosis and the subjects with poor compliance. Subjects may withdraw their informed consent at any time during the study without discrimination.

3.2.4 Enrollment Time

From the date of ethics approval

3.2.5 Expected Overall Duration of the Clinical Study

Six years

3.2.6 Number of Subjects Required for Clinical Study

40 cases

3.3 Study Endpoint

3.3.1 Primary Study Endpoint

Complete response rates after CD19 CAR-T cell therapy

3.3.2 Secondary Study Endpoints

1） Overall response rate (ORR = CR + PR) according to Lugano 2014 criteria;

2） Duration of remission (DOR);

3） PFS and OS;

4） Safety

5） Characteristics of relapse (including expression of CD19 and CD20)

3.3.3 Exploratory Study Endpoints:

The expansion and persistence of CAR-T cells in vivo and the clearance of B cells.

4 Research Process

4.1 Bridging Scheme

Before CAR-T cell therapy, a three-drug bridging therapy consisting of "Zanubrutinib + lenalidomide + CD20 monoclonal antibody" was given for 2 cycles. The regimen was as follows: intravenous rituximab 375 mg/m² on day 1, oral lenalidomide 25 mg daily on days 1 to 21, and continuous oral Zanubrutinib 160 mg twice daily in each 28-day cycle).

4.2 Pre-Treatment Evaluation of CAR-T Cell

After the completion of 2 cycles of bridging therapy, the efficacy was evaluated by PET-CT, and the patients with CR, PR or SD efficacy evaluation compared with the baseline were enrolled in CAR-T cell therapy, and the patients with PD efficacy evaluation were excluded from the group and did not receive CAR-T cell therapy.

4.3 Cell Source

The CD19 CAR-T cells in this study were derived from the subject's own T cells and were prepared by Shanghai Yake Biotechnology Co., Ltd.

4.4 Apheresis

Subjects who meet the enrollment requirements will be subjected to peripheral blood mononuclear cell apheresis for the production of CAR-T cell drugs, with the goal of collecting no less than 1×10^9 mononuclear cells.

4.5 Lymphodepletion

4.5.1 Lymphodepletion Evaluation

The investigator should assess the tumor burden of the subject prior to lymphodepletion. The infection and immune status should be evaluated according to the actual situation. For patients with uncontrolled systemic infection, the relevant procedures after enrollment should be suspended, and the timing of lymphodepletion and infusion should be reassessed.

4.5.2 Lymphodepletion Scheme

After apheresis and before infusion of CAR-T cell, subjects need FC (fludarabine + cyclophosphamide) lymphodepletion, specifically:

Fludarabine: 30 mg/m^2/d, intravenous infusion, once a day, from -4 to -2 days, for 3 consecutive days;

Cyclophosphamide: 500 mg/m^2/d, intravenous infusion, once a day, from -3 days to -2 days, for 2 consecutive days. (The investigator will assess the subject's status and determine the specific dose to be administered); the treatment begins with an intravenous infusion of cyclophosphamide within 30 minutes, followed by an intravenous infusion of fludarabine.

CAR-T cell infusion was performed on Day 0 after lymphodepletion, and in special cases, the investigator could select the opportunity for CAR-T cell therapy according to the change of the subject's condition.

Lymphodepletion regimen calculation formula:

BSA (m^2) = 0.0061 × height (cm) + 0.0128 × weight (kg) -0.1529;

Fludarabine (mg) = BSA × 30mg/m^2

Cyclophosphamide (mg) = BSA × 500 mg/m^2

The body surface area (BSA) of the subjects was calculated according to the latest height and weight before lymphodepletion, and it was appropriate to calculate BSA according to the height and weight measured the day before pretreatment.

4.5.3 Evaluation After lymphodepletion

After the lymphodepletion, the investigator should evaluate the subject according to the actual situation, including tumor burden, immunity, infection, etc. If there is any situation that is not suitable for infusion, it should be considered to suspend or terminate the use of CAR-T.

4.5.4 CD19 CAR-T Cell infusion

CAR-T cell therapy was performed one day after the lymphodepletion (day 0), and in special cases, the investigator could choose the opportunity to perform CAR-T cell therapy according to the change of the subject's condition. The target dose of CAR-T infusion is 2 × 10^6 CAR-positive T cells/kg (dose range ± 20%), and the minimum acceptable dose in special cases is 1 × 10^6 CAR-positive T cells/kg.

4.6 Study Drug

4.6.1 Quality Control of CAR-T Cell Preparation

① Quality control of preparation materials

The materials used in the preparation process shall conform to the principle of aseptic safety, and a complete registration and monitoring system for the preparation of materials shall be established, and the

detection items of corresponding safety and utility properties shall be set up, such as the detection of bacteria, fungi, mycoplasma and exogenous virus contamination, and the detection of purity, potency and other tests related to cell activation and proliferation.

② Quality control of plasmid vector and viral vector

The quality control of the plasmid vector: the plasmid in the strain is proved to contain the target element and the corresponding copy number by detecting the plasmid sequence, the copy number and the restriction enzyme cutting map; The retention rate of plasmids was tested to verify the stability of the strain and to limit the level of passage used by the strain. The purity control of plasmid includes two aspects; one is the quality of plasmid itself. On the other hand, it is the control of process impurities, such as host bacteria protein residues, host bacteria DNA residues and other ingredients added in the process that need to be controlled.

Quality control of viral vectors: viral vectors need to evaluate the titer of the vector, and the ability to transduce cells is usually used as the titer of the viral vector. In addition, the detection items of exogenous factor contamination were carried out for each batch of viral vectors, including bacteria, fungi, mycoplasma and exogenous viral factor contamination.

③ Production quality control of CAR-T cells: After the preparation of CAR-T cells, it is necessary to detect the number of cells, cell survival rate, positive rate of cell phenotype CAR, biological efficacy and safety.

4.6.2 CAR-T Cell Infusion Environment

The environment for CD19 CAR-T cell infusion of the investigational product in this study is based on the requirements of routine clinical transfusion environment.

4.6.3 Medication Method and Precautions

The study drug is CAR-T cell preparation for intravenous infusion, and the specific use method refers to the following requirements (taking the frozen product as an example):

① At 37 ℃, the CAR-T cell preparation was thawed with normal saline until there was no visible ice in the infusion bag.

② Check whether there are any visible cell clumps in the contents of the thawed infusion bag. If they still exist, gently mix the contents of the bag. Small clumps of honeycomb material can be broken up by hand. The product shall not be infused in case of undispersed mass, damage of infusion bag, leakage or other abnormal conditions, and the investigator shall contact Shanghai Yake Biotechnology Co., Ltd. in time to provide new cell preparations.

③ Once CAR-T has been thawed and is at room temperature (20℃ to 25℃), the infusion should be completed within 30 minutes. Do not wash or resuspend CAR-T cells with a new solution before infusion.

④ The recommended infusion rate of CAR-T was 20 to 40 drops per minute, and the researchers could adjust the infusion rate according to the condition of the subjects. Attention should be paid during infusion:

white blood cell filters should not be used;

Rinse the tubing with saline prior to infusion;

Filling all the contents in the infusion bag;

Flush the bag with 10 mL to 30 mL of normal saline while the tubing is closed to ensure that as much of the contents of the bag as possible are infused into the patient.

4.6.4 Premedication Evaluation

Before the subject is administered with the study drug, the investigator shall further confirm the immunity, infection, tumor burden and concomitant medication according to the actual situation, and consider suspending or terminating the use of the study drug in case of any inappropriate infusion.

For example, CAR-T cell preparations should not be infused for 72 hours following the use of large amounts of glucocorticoids (without physiologic replacement therapy) prior to infusion.

4.7 Research Process

4.7.1 Pharmacokinetic Study

In order to fully study the expansion and persistence of CAR-T cells in the subjects, the pharmacokinetic study will be continued in this trial. The main observation indexes are peak concentration, peak time and T cell persistence time. The monitoring methods are as follows:

1) Flow cytometry

Detection principle: combination of antigen-antibody system and flow cytometry

2) Quantitative real-time polymerase chain reaction

Detection principle: The amplification efficiency is monitored by the external standard method, the number of starting templates is accurately quantified, and the false negative results are excluded by the internal control (the amplification efficiency is zero). In addition to the above analysis methods, if necessary, other validated detection methods may be used to dynamically monitor the changes of CAR-T cells in vivo. CAR-T shall be monitored from 1 day before cell infusion to the end of the treatment observation period, during which pharmacokinetic indicators shall be observed at each visiting point; after entering the survival follow-up period, subjects shall be continuously monitored, and the end point of pharmacokinetic monitoring is that CAR-T cannot be detected in vivo, that is, the results of two consecutive monitoring are negative.

4.7.2 Research Process

In this study, the screening period was within 14 days, the bridging treatment period was about 60 days, the cell preparation and lymphodepletion period was about 15 days, the CAR-T treatment observation period was 30 days, and the CAR-T treatment follow-up period was 60 days.

After 90 days of CAR-T infusion, patients entered the survival follow-up period, and the recent safety follow-up was until CAR-T cells were not detected in vivo or 2 years after infusion, whichever was longer. Because of the potential tumorigenicity of CAR-T cell preparations, long-term safety follow-up should be lifelong or at least 15 years for tumorigenicity.

1) Screening period (within 14 days before enrollment, V1)

After signing the informed consent form, the following examinations and evaluations shall be completed within 14 days, and whether to be included in the group shall be determined:

Signed informed consent;

Demographic information: sex, date of birth, ethnicity, occupation, marriage;

Medical history confirmation, including: history of LBCL and related treatment; history of other malignant tumors; Other medical history (including but not limited to: cardiopulmonary disease, mental disorder, active autoimmune disease, active infectious disease, etc.);

Vital signs: body temperature, respiration, heart rate (or pulse), blood pressure, height, weight;

Physical examination: general condition, skin and mucous membranes, lymph nodes, head, neck, chest, heart, abdomen, genitourinary system, spine, limbs, nervous system, mental condition, and others; Height and weight;

Blood routine: white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), platelet count (PLT), absolute value of neutrophil (Neut #), absolute value of lymphocyte (Lymph #), absolute value of monocyte (Mono #);

Coagulation function: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT);

Blood biochemistry:

Electrolyte: potassium (K), sodium (Na), chlorine (Cl), calcium (Ga), phosphorus (P), magnesium (Mg);

Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), total protein (TP), albumin (ALB), globulin (GLOB), total bilirubin (TBIL), lactate dehydrogenase (LDH);

Renal function: Urea, SCr, UA, GFR or Ccr;

Blood lipid: total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL-C), low density lipoprotein (LDL-C);

Blood glucose (GLU);

Echocardiography: left ventricular ejection fraction (LVEF);

Virological examination: including hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), Treponema pallidum (TP), Epstein-Barr virus (EBV), cytomegalovirus (CMV); If the antigen-antibody screening method is not clear, the nucleic acid method should be used for confirmation. If the HCV, EBV and CMV antigen-antibody screening method is positive, the nucleic acid method should be added, that is, HCV-RNA, EBV-DNA and CMV-DNA. If HBsAg and HBeAg are positive, HBV-DNA should be added. The above virology items can accept the examination results within one month before enrollment, except HIV.

ECOG score;

Pregnancy screening: Pregnancy screening is required for all women of gestational age (including tubal ligation) during the screening period;

Lymphoma biopsy pathology: including the expression of CD19 and CD20, and the rearrangement of C-MYC/BCL-2/BCL-6 detected by FISH or next-generation sequencing;

Bone marrow examination: bone marrow smear observation and flow cytometry;

Imaging examination: PET-CT;

Rheumatism immune examination: qualitative examination of antinuclear antibody (ANA);

Urine routine:

Urine chemistry: urobilinogen (UBG), bilirubin (BIL), ketone body (KET), occult blood (ERY), urine protein (PRO), glucose (GLU), pH, vitamin C (VC), urine specific gravity (SG);

Microscopic examination of urine sediment: red blood cell (RBC), white blood cell (WBC);

12-lead electrocardiogram;

Immunoglobulin: complement C3, complement C4, immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM);

Ferritin;

C-reactive protein;

Procalcitonin (PCT);

Cardiac enzymes: B-type natriuretic peptide (BNP) or pro-peptide of B-type natriuretic peptide (NT-proBNP);

Lymphocyte subsets: CD3, CD4, CD8, CD16, CD45, CD56;

Estimated survival time assessment;

Adverse events;

Concomitant medication.

Unless otherwise required, the above inspections and contents are the same as the following.

According to the above examination results, the inclusion/exclusion criteria were checked one by one, and the investigator confirmed whether the screened patients were enrolled. In the screening process, if there are enough strong materials to prove that patients do not meet the requirements of enrollment, the examination items that have not been carried out may not be carried out.

2) Bridging Treatment period (about 60 days after enrollment, V2)

The patient was treated with 2 28-day cycles of ZR^{2}regimen, each cycle as follows:

Week 1 to 2

Twice a week: blood routine, blood biochemistry;

Once a week: vital signs; physical examination; coagulation function; Myocardial enzymes; C-reactive protein.

Weeks 3 to 4

Once a week: vital signs; physical examination; blood routine; blood biochemistry; coagulation function; Myocardial enzymes; C-reactive protein;

D60: PET-CT.

3) Cell preparation and lymphodepletion period, V3

Cell preparation

For the subjects who received bridging therapy and whose efficacy was evaluated as SD or above, peripheral blood mononuclear cells should be collected, and CAR-T cell preparations should be prepared by Shanghai Yake Biotechnology Co., Ltd.

Lymphodepletion period

The following tests were performed prior to lymphodepletion, including:

Vital signs; Physical examination; Blood routine; Coagulation function; Blood biochemistry; Echocardiography; Viral examination; Urine routine; Immunoglobulin; Ferritin; C-reactive protein; Procalcitonin; Cardiac enzymes; Cytokines; Lymphocyte subsets; T cell subsets; CAR-copy; Adverse events; Concomitant medication.

Cytokines include IL-2 and IL-6 (the same below), and T cell subsets include CAR, CD3, CD4 and CD8 (the same below).

After apheresis and before infusion of cell preparations, the investigators selected the opportunity to carry out FC lymphodepletion according to the condition of the subjects.

3) Treatment observation period (D0 ~ D30)

The day on which the subject received the first intravenous infusion of CAR-T cell preparation was recorded as D0, and the subject was followed up for 30 days during the treatment observation period, and the corresponding items were examined to evaluate the effectiveness and safety of the cell preparation treatment.

D0(V4)

Keywords Vital signs; Physical examination; Cytokines; Lymphocyte subsets; T cell subsets; CAR-copy; Adverse events; Concomitant medication.

Among them, in addition to height and weight, physical examination only needs to record significant changes compared with baseline (the same below).

D4(V5)、D7(V6)、D9(V7)、D11(V8)、D14(V9)、D21±1(V10)

Keywords Vital signs; Physical examination; Blood routine; Coagulation function; Blood biochemistry; Urine routine; Immunoglobulin; Ferritin; C-reactive protein; Procalcitonin; Myocardial enzymes; Cytokines; Lymphocyte subsets; T cell subsets; CAR-copy; Adverse events; Concomitant medication.

D30±1(V11)

Vital signs; physical examination; blood routine; coagulation function; blood biochemistry; urine routine; 12-lead electrocardiogram; immunoglobulin; ferritin; C-reactive protein; procalcitonin; cardiac enzymes; cytokines; lymphocyte subsets; T cell subsets; CAR copies; PET-CT; Adverse events; Concomitant medication.

4) Treatment follow-up period (D31-D90)

After the completion of the treatment observation period, the investigator still needs to follow up the effectiveness and safety of the CAR-T treatment (60 days in total) and complete the corresponding examination.

D60±3(V12)

Keywords Vital signs; Physical examination; Blood routine; Coagulation function; Blood biochemistry; Urine routine; Immunoglobulin; Ferritin; C-reactive protein; Procalcitonin; Myocardial enzymes; Cytokines; Lymphocyte subsets; T cell subsets; CAR-copy; Adverse events; Concomitant medication.

D90±3(V13)

Vital signs; physical examination; blood routine; coagulation function; blood biochemistry; echocardiography; ECOG score; urine routine; 12-lead electrocardiogram; immunoglobulin; ferritin; C-

reactive protein; procalcitonin; cardiac enzymes; cytokines; lymphocyte subsets; T cell subsets; CAR copies; PET-CT; Adverse events; Concomitant medication.

Gestational age women also need to do: pregnancy tests.

Before the end of the treatment follow-up period, if early withdrawal occurs, the subject should complete the pre-withdrawal visit and evaluation as far as possible. Patients who withdraw early or terminate the study should complete the Early Withdrawal Visit as soon as possible (within 1 week of withdrawal), as required by V13, and should complete the visit and evaluation prior to receiving the new treatment.

5) Survival follow-up period (after D90)

After the treatment follow-up period, the subject entered the survival follow-up period. According to the persistence of CAR-T cell in the patient, the investigator advised the subject to follow up in a timely manner and improve the pharmacokinetic monitoring at least once every three months until two consecutive negative test results or death occurred.

In addition, for the patients in the survival follow-up period, the researchers carried out regular follow-up, once every 3 months within 2 years after CAR-T infusion, and once every 6 months within 2-5 years after CAR-T infusion, to understand their physical and living conditions, collect follow-up treatment data, and record the details of follow-up as detailed as possible. Long-term safety follow-up, subject to tumorigenicity for life or up to 15 years.

The following information should also be obtained during follow-up throughout the survival period:

1) assessment of survival time, including the date of assessment;

2) In case of death, the date of death shall be recorded;

3) All new cancers.

Study-related safety follow-up should also continue during the survival follow-up period until the follow-up endpoint for adverse events is reached.

Throughout the study, the investigator may increase or decrease the examination items or visiting points according to the clinical practice, but the reasons for the increase or decrease should be recorded as far as possible. If the same inspection item is performed several times at the same visit point due to the need of research, the results of the first inspection shall be taken as the main research data, and other inspections shall also be recorded.

Table 1 Flow chart of clinical study

Pilot Phase *	**Screening Period[a]**	**Bridging Treatment Period (2 28-day cycles, each as follows)**		**Cell preparation and lymphodepletion period**	**Treatment Observation Period[b]**								**Treatment follow-up period[b]**		**Survival follow-up period[c]**
Diagnosis and treatment/evaluation project	**Within 14 days prior to enrollment**	**Week 1-2**	**Weeks 3-4**	**About 15 days**	**0**	**4**	**7**	**9**	**11**	**14**	**21±1**	**30±1**	**60±3**	**90±3**	**After 90**
Visit point	**V1**	**V2**		**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**---**
Informed consent	●														
Demographic Information[1]	●														
Medical History[2]	●														
Vital Signs[3]	●	Once a week	Once a week	●	●	●	●	●	●	●	●	●	●	●	●
Physical examination[4]	●	Once a week	Once a week	●	●	●	●	●	●	●	●	●	●	●	●
Blood routine[5]	●	Twice a week	Once a week	●		●	●	●	●	●	●	●	●	●	●
Coagulation[6]	●	Once a week	Once a week	●		●	●	●	●	●	●	●	●	●	
Blood biochemistry[7]	●	Twice a week	Once a week	●		●	●	●	●	●	●	●	●	●	●
Echocardiogram[8]	●			●										●	
Virological examination[9]	●			●											
ECOG score	●													●	
Pregnancy test[10]	●													●	
Pathological examination of lymphoma[11]	●													●	
Bone marrow examination[12]	●		When necessary									When necessary		When necessary	
Imaging[13]	●		●D60									●		●	When necessary
Rheumatism immune test[14]	●														
Urine routine[15]	●			●		●	●	●	●	●	●	●	●	●	
12-lead electrocardiogram	●			●								●		●	
Immunoglobulin[16]	●			●		●	●	●	●	●	●	●	●	●	●
Ferritin	●			●		●	●	●	●	●	●	●	●	●	
C-reactive protein	●	Once a week	Once a week	●		●	●	●	●	●	●	●	●	●	●
Procalcitonin	●			●		●	●	●	●	●	●	●	●	●	
Myocardial	●	Once a week	Once a week	●		●	●	●	●	●	●	●	●	●	●

enzyme[17]															
Cytokine[18]				●	●	●	●	●	●	●	●	●	●	●	
Lymphocyte subsets[19]	●			●	●	●	●	●	●	●	●	●	●	●	
Estimated survival assessment	●														
Entry and discharge verification	●														
Apheresis and preparation				●											
Chemotherapy pretreatment				●											
CAR Copy[20]				●	●	●	●	●	●	●	●	●	●	●	●
T cell subsets[21]				●	●	●	●	●	●	●	●	●	●	●	●
CAR-T infusion					●										
Adverse Event [I]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Concomitant Treatment/Medication[II]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

Note 1:

a) Screening regulations: 1) If the patient has enough strong materials to prove that he meets the enrollment requirements during the screening period, the rest of the evaluation items in this study can not be carried out;

b) Subjects who withdraw or terminate the study early during the study should try to complete the early withdrawal visit as soon as possible within one week;

c) For the subjects in the survival follow-up period, according to the persistence of CAR-T cell in the patients, the investigator advised them to follow up in time and improve the pharmacokinetic monitoring, at least once every three months, until two consecutive test results showed negative or 2 years after infusion; After that, for the patients during the survival follow-up period, the investigators carried out regular follow-up, once every 3 months for 2 years after CAR-T infusion, and once every 6 months for 2-5 years after CAR-T infusion.

Note 2:

1. Demographic information: sex, date of birth, ethnicity, occupation, marriage;
2. History: 1) history of large B-cell lymphoma; 2) history of other malignancies; 3) Other medical history (including but not limited to: cardiopulmonary diseases, mental disorders, active autoimmune diseases, active infectious diseases, etc.);
3. Vital signs: respiration, heart rate (or pulse), body temperature, blood pressure; blood oxygen saturation observation should be added before and after cell preparation infusion;
4. Physical examination: general condition, skin and mucosa, lymph nodes, head, neck, chest, heart, abdomen, genitourinary system, spine, limbs, nervous system, mental status and other comprehensive examinations are required during the screening period and D-1. After that, only significant changes need to be recorded in the physical examination. Height and weight were measured according to the visiting requirements;
5. Routine blood test: white blood cell count, red blood cell count, hemoglobin, platelet count, absolute value of neutrophil, absolute value of lymphocyte, absolute value of monocyte;
6. Coagulation function: prothrombin time, international normalized ratio, activated partial thromboplastin time;
7. Blood biochemistry: 1) electrolytes: potassium, sodium, chlorine, calcium, phosphorus, magnesium; 2) liver function: alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, total protein, albumin, globulin, total bilirubin, lactate dehydrogenase; 3) renal function: urea, serum creatinine, uric acid, glomerular filtration rate GFR or creatinine clearance rate Ccr; 4) total cholesterol, triglyceride, high density lipoprotein and low density lipoprotein; 5) Blood glucose;
8. Echocardiography: left ventricular ejection fraction (LVEF);

9. Virological examination: HBV, HCV, HIV, TP, EBV, CMV virological antibody examination; if HCV, EBV, CMV virological antibody screening is positive, nucleic acid quantitative examination should be added, i.e. HCV-RNA, EBV-DNA, CMV-DNA; If HBsAg and HBeAg are positive in two half-and-half pairs of hepatitis B (HBsAg, HBsAb, HBeAg, HBeAb, HBcAb), they should be tested by nucleic acid method, that is, HBV-DNA; the test results within one month before the above screening are acceptable, except for HIV;
10. Pregnancy screening: pregnancy screening is required for all women of gestational age (including tubal ligation); pregnancy screening is required at the end of study/early withdrawal termination visit;
11. Pathological examination of lymphoma: positive expression rate of CD19 and CD20 in tumor tissue; The rearrangement of C-MYC/BCL-2/BCL-6 was detected by FISH or next-generation sequencing.
12. Bone marrow examination: bone marrow MRD examination and/or bone marrow smear examination;
13. Imaging examination: PET-CT;
14. Rheumatism immune examination: qualitative examination of antinuclear antibody (ANA);
15. Urine routine: 1) Urine dry chemistry: urobilinogen, bilirubin, ketone body, occult blood, urine protein, urine glucose, uric acid alkalinity, urine specific gravity, vitamin C; 2) Microscopic examination of urine sediment: red blood cells and white blood cells;
16. Immunoglobulin: complement C3, complement C4, immunoglobulin A, immunoglobulin G, immunoglobulin M;
17. Cardiac enzymes: B-type natriuretic peptide or pro-peptide of B-type natriuretic peptide;
18. Cytokines: IL-2, IL-6, etc. The researcher can add necessary factor tests as needed;
19. Lymphocyte subsets: CD3, CD4, CD8, CD16, CD45, CD56, etc.
20. CAR copy and Q-PCR: can be detected according to the clinical research center;
21. T cell subsets: CAR, CD3, CD4, CD8, etc., which can be sent to a third party for testing according to the testing situation of the clinical research center;

For the above examinations, the investigator can make necessary increase or decrease according to the actual situation of the patient, but the reasons for the increase or decrease should be recorded.

For the above inspections, if the same inspection item is executed for many times at the same visiting point, the results of the first inspection shall be taken as the main research data, and the results of other inspections shall also be recorded truthfully.

Note 3:

I Requirements for adverse events: 1) Record all AEs and report SAEs from the beginning of the screening period; 2) When the subject withdraws from the trial, the outcome of adverse events should be tracked as far as possible until the end of AE follow-up; 3) During the survival follow-up period, AEs related to this study were recorded and SAEs related to this study were reported;

II Requirements for concomitant treatment/medication: 1) Record all concomitant medications and treatments from the beginning of screening to the treatment follow-up period; 2) When the subject withdraws or enters the survival follow-up period, the concomitant medication and treatment related to the study shall be recorded. If other anti-tumor interventions occur, the latest intervention shall be recorded.

4.8 Ethics and Informed Consent

4.8.1 Good Clinical Practice

The actions listed in this clinical trial protocol regarding the conduct, evaluation, and documentation of this study are intended to ensure that its authorized representatives and investigators comply with the fundamental ethical requirements listed in the GCP regulations and the Declaration of Helsinki. The approval of the ethics committee should be obtained before the start of the trial. The investigator shall comply with the applicable regulatory requirements of national, provincial and local regulatory authorities in all aspects of the performance of the trial.

4.8.2 Responsibilities of the Investigator

The responsibilities of the investigator are defined in the GCP and local regulatory requirements. The researcher should be authorized to carry out relevant work. The investigator shall ensure that all personnel assisting in the conduct of the study are fully informed of the study protocol and its amendments, the course of study treatment, and the responsibilities and functions associated with the study. The investigator should maintain a list of assistant investigators and other personnel with appropriate qualifications who have undertaken significant assignments related to the study.

The investigator is responsible for maintaining a record of all subjects who have signed the informed consent form and passed the screening for study entry. For subjects who fail screening, the reason for the failure must be documented in the subject's source file.

During the monitoring visit, the investigator or his/her designated staff must be present to review the data, resolve queries, and have direct access to subject records (e.g., medical records, outpatient record sheets, hospital record sheets, and study-related record sheets) to verify the raw data. Investigators must ensure that CRFs and data challenges are completed in a timely and accurate manner.

4.8.3 Ethics Committee

The trial shall not be started until the trial protocol and informed consent have been approved by the ethics committee (EC). The EC shall be constituted in accordance with the requirements of the NMPA and shall perform all the duties specified.

4.8.4 Related Tables

The forms involved in the clinical trial are subject to EC requirements.

4.8.5 Ethics Approval Document

Before the start of the study, the investigator shall submit the study protocol, informed consent, CRF, approval documents of relevant authorities, and any advertisement of the recruited subjects to the ethics committee of the clinical research leader unit or the independent ethics committee of other clinical research units for approval. Only after receiving the ethical approval, the investigator can enroll the case. If the test protocol needs to be changed later, it must be submitted to EC for review. The trial can be continued only after the content of the protocol changes and the revised informed consent form have been reviewed and approved by EC.

4.8.6 Informed Consent

The informed consent form must be submitted to the relevant ethics committee for approval, and the benefits and risks of the trial must be fully explained to each potential subject before they participate in any activities related to the trial. After explaining the basic content of the trial and ensuring that each subject who will participate in the trial has understood the purpose of the trial, the investigator shall ask each subject who will participate in the trial to sign and date the informed consent form. The informed consent was made in duplicate, one for the investigator and one for the subject. In addition, if important new data related to the investigational drug are found, the informed consent must be revised in writing and submitted to the ethics committee for approval, and then the consent of the subjects shall be obtained again. All ICF versions approved by the ethics committee are required to be signed by current participants and used for future recruitment.

4.8.7 Subject Privacy

It is the responsibility of the investigator and the collaborating entity to respect the privacy of the subject and respect the confidentiality of the records.

4.9 Subject Screening

Subjects will sign an informed consent form prior to enrollment in the study. The investigator will explain the nature, purpose, and risks of the study and provide the subject with a copy of the informed consent form. Subjects will be given sufficient time to consider the implications of the study before deciding whether to participate in the study. Any changes to the informed consent form required ethical notification and approval prior to enrollment.

First, the subjects need to go through the informed consent process and sign the informed consent form, and then according to the pre-established inclusion and exclusion criteria of this study, the subjects who meet the criteria are screened from the target population before they can be considered to be included in this study.

The general examination, medical history, laboratory tests, and ECG data of the subject in the hospital or outside the hospital within one week before signing the informed consent form can be collected as the baseline value. Adverse events and concomitant medication need to be collected after signing informed consent.

5 Statistical Considerations

5.1 Statistical Overview

In order to comply with the clinical trial protocol, the Good Clinical Practice of the People's Republic of China, the smooth implementation of the trial, the generation, recording and reporting of relevant data, and to ensure the credibility of all data related to the clinical trial and the rationality of its processing, quality management will be implemented at all stages of data processing. All data related to clinical trials are processed and analyzed by specialized biostatisticians.

5.2 Sample Size and Its Justification

The sample size was estimated using Power Analysis and Sample Size 15.0 software (NCSS, Kaysville, UT, USA). In the phase III GOYA trial(15) comparing G-CHOP versus R-CHOP in previously untreated DLBCL patients with higher-risk features (IPI≥2, or IPI=1 in patients <60 years with/without bulky disease, or IPI=0

with bulky disease), neither treatment arm achieved the prespecified CR rate of 60% (56.5% with G-CHOP and 59.1% with R-CHOP). Therefore, a CR rate of 70% was assumed to represent a clinically meaningful improvement over standard chemoimmunotherapy in high-risk LBCL.

This single-arm study was designed to estimate the CR rate in high-risk LBCL patients treated with ZR^2 regimen sequential to CD19 CAR-T therapy, with a target CR rate of 70%. Under the Clopper-Pearson method, a sample size of 40 subjects would yield an 80% confidence interval (CI) for the response rate with a maximum width of 0.21 when the observed CR rate is 70%, corresponding to a lower limit of at least 58.8%. This target and the lower bound of the 80% CI were considered clinically meaningful, as they would reflect a substantial improvement over available therapy.

5.3 Significance and Power of Clinical Research

The significance level α is taken as 0.05, and the power 1-β is taken as 0.8.

5.4 Statistical Analysis of Population and Statistical Methods

5.4.1 Statistical Analysis of the Population

1) Treated population/Safety population: All patients who received at least one dose of study treatment including ZR^2 bridging treatment.
2) Evaluable for efficacy population: All patients who have at least one post treatment efficacy assessment.
3) PK analysis population: All patients who received partial or full CAR-T cells infusion and have at least 1 reportable post treatment PK concentration

5.4.2 Statistical Analysis Method

All statistical analyses are processed by statistical software, and the designed statistical analysis set is completed according to the statistical analysis plan. The description of quantitative indicators will calculate the mean, standard deviation, median, minimum and maximum values.

The number of cases and percentage of each category are used to describe the classification index.

5.5 Handling of Missing Values and Outliers

Handling of missing values: Delete missing values

Processing of abnormal values: the abnormal values are regarded as missing values and are processed according to the missing value processing method

5.6 Expected Dropout Rate

10%

6 Data Recording and Management

6.1 Case Report Form

A CRF was required for each subject who signed the informed consent form.

The Collaborator or its client will provide the CRF to the Research Center. CO-PARTNER will arrange for training of staff in the study site on the use of CRF. The CRF shall be filled out by the investigator or the person designated by the investigator according to the original case, and shall not be altered at will. If modification is

required, standard operation shall be carried out according to the CRF filling instructions, and the name of the modifier and the date of modification shall be signed. The investigator at each center is required to verify the information in each CRF to ensure its accuracy and authenticity, and to sign the name and date of verification. The investigator is fully responsible for the accuracy and validity of all data entered into the CRF. The Principal Investigator is required to review the CRF for completeness and accuracy and to sign and date the CRF as directed.

The CRF will be reviewed for completeness and acceptability during the monitor's periodic visits to the site. The partner or its client shall allow the monitor to review the medical and hospitalization records related to the study to ensure the accuracy of the CRF. The completed CRF is the sole property of the Partner and shall not be disclosed in any form to a third party without the prior written consent of the Partner, except to authorized representatives of the relevant governmental health or competent authorities.

6.2 Record Keeping

The investigator agrees to maintain records as agreed, including (but not limited to) study-specific documents, all subject identification sheets, medical records, temporary media (e.g., thermal paper), original worksheets, all signed and dated original informed consent forms, detailed medication record sheets, For evaluation and audit by regulatory authorities, partners or their clients. Any source documents printed on degradable thermal paper shall be photocopied at the site and filed with the original documents in the subject's medical record to ensure that they are legible over long periods of storage. In addition, Section 4.9.5 of International Conference on Harmonization (ICH) E6 requires the investigator to maintain the critical documentation specified in ICH E6 (Section 8) until at least 2 years after final approval of the marketing application for the investigational drug indication or, if the application is not approved, until 2 years after discontinuation of the study and notification to the regulatory authority. In addition, study records may be kept for more than 2 years, as required by applicable regulations or by agreement with the partner.

Please refer to the Clinical Study Agreement for the requirements of the Partner regarding record keeping. Before processing any of these documents, the investigator shall first contact the collaborator and obtain the written approval of the collaborator.

6.3 Source File

According to the requirements of relevant laws and regulations, the investigator shall properly keep the original records of the clinical study. The investigator must keep the study protocol, CRF, relevant correspondence with the collaborator and other trial documents until 5 years after the end of the study, or until the collaborator notifies the investigator to destroy these documents.

7 Criteria and Procedures for Clinical Study Termination

Discontinuation of the study means that the clinical study is not completed according to the protocol and all studies are stopped halfway. The main purpose is to protect the rights and interests of subjects and ensure the quality of research. See 3.2.3 for details.

8 Study the Expected Progress

Duration of study recruitment: 60 months

Observation period: 2 years

9 Assessment and Reporting of Adverse Events

9.1 Definition of Adverse Event

9.1.1 Adverse Events (AEs)

Any adverse medical event, including symptoms, signs, or laboratory abnormalities, that occurs during or after a subject's treatment in a clinical study that is not related to the intended therapeutic effect.

Abnormal laboratory values or test results occurring after informed consent constitute an AE only if they cause clinical signs or symptoms that are clinically significant, require treatment (e.g., hematologic abnormalities requiring blood transfusion or hematopoietic stem cell support), or require a change in the dose of the investigational product.

9.1.2 Serious Adverse Events (SAEs)

A serious adverse event was defined as an adverse event that occurred in any phase of the study (before treatment, during treatment, and during follow-up) that met one or more of the following criteria: death, fatal illness or injury, rehospitalization or prolonged hospitalization, disability, teratogenesis resulting in loss of independence, and congenital malformation.

Serious medical event: may endanger the subject or may require medical intervention to prevent the occurrence of the above condition. The investigator is required to evaluate each adverse event or complication that meets the above criteria and report back to the study sponsor. The investigator shall report the adverse event and its subsequent progress and treatment. All adverse events: Any event that does not meet any of the criteria for a serious event will be considered non-serious.

9.1.3 Major Adverse Events

9.1.3.1 Cytokine Release Syndrome (CRS)

Cytokine-associated toxicity, also known as cytokine release syndrome, is caused by intense immune activation. If immunotherapy is to produce the desired clinical efficacy, the intensity of immune activation used will exceed the intensity of immune activation in the general natural state. Recent studies have shown that the incidence and intensity of CRS are positively correlated with tumor burden, possibly because larger tumor burden can lead to higher levels of T cell activation. Symptoms of CRS usually appear several days after the infusion of T cells and may appear several weeks later. In conclusion, the time point of the onset of CRS symptoms coincides with the time point of peak T-cell expansion in vivo. CRS can cause a wide range of symptoms with varying degrees of severity. Relevant clinical signs and symptoms include:

1) Complex symptoms: fever (possibly accompanied by chills), listlessness, fatigue, anorexia, muscle pain, arthralgia, nausea, vomiting, headache;

2) Skin: rash;

3) Gastrointestinal: nausea, vomiting, diarrhea;

4) Respiratory system: shortness of breath, hypoxemia;

5) Cardiovascular: tachycardia, wide pulse pressure, hypotension, increased cardiac output (early stage), decreased cardiac output (late stage);

6) Coagulation: elevated D-dimer, hypofibrinogenemia (possibly with bleeding);

7) Kidney: azotemia;

8) Liver: transaminase inflammation, hyperbilirubinemia;

9) Nervous system: headache, altered mental status, confusion, unconsciousness, speech difficulties or aphasia, hallucinations, tremors, dysmetria, gait changes, epilepsy

10) Complications of CRS with potentially fatal consequences include cardiac dysfunction (cardiac insufficiency, respiratory and cardiac arrest, malignant arrhythmias), adult respiratory distress syndrome, neurotoxicity, renal and/or hepatic failure, cerebrovascular accident, disseminated intravascular coagulation, and other unpredictable complications.

CRS grading system

Grading	**Toxicity index**
Level 1	No life-threatening critical symptoms, and only symptomatic treatment is needed. Examples of symptoms: fever, nausea, fatigue, headache, muscle pain, listlessness
Level 2	Symptoms requiring moderate treatment: oxygen demand < 40% or hypotension relieved by fluids or 1 low dose of vasopressor or grade 2 tissue organ toxicity
Level 3	Symptoms requiring moderate treatment: oxygen demand ⩾ 40% or hypotension requiring relief by 1 high dose of vasopressor or multiple vasopressors or grade 3 tissue organ toxicity or grade 4 transaminase elevation
Level 4	Life-threatening critical symptoms: need to use ventilator or grade 4 tissue and organ toxicity (excluding transaminase elevation)
Level 5	Death

CRS Response:

1) For Level 1 CRS:

A. Preventative supportive treatment may be used.

B. Infection assessment: treat possible fever and neutropenia, monitor fluid balance, and use antipyretics and analgesics if necessary.

2) Level 2 CRS in non-elderly subjects without multiple complications: prophylactic supportive treatment and close monitoring of cardiac and other organ function may be used.

3) For level 2 CRS with multiple complications or in elderly subjects, level 3, or level 4 CRS:

A. Preventative supportive treatment may be used;

B. Tocilizumab (4 mg/kg for adults), an anti-interleukin-6 antibody, should be administered for more than 1 hour, and if the clinical signs and symptoms do not resolve within 24-48 hours after administration, repeat dosing may be considered.

C. Cooperate with corticosteroid therapy as appropriate. Methylprednisolone 2 mg/kg/day may be used and may be discontinued after a few days. Dexamethasone (0.5 mg/kg, up to 10 mg per dose) may be considered for subjects with severe neurotoxicity. Risk prevention measures include exclusion of contraindications, strict treatment procedures and norms, close monitoring of vital signs and indicators, appropriate treatment by doctors according to the condition, symptomatic treatment.

9.1.3.2 Hypogammaglobulinemia and Related Complications

After cell infusion, CAR-T cells attack tumor B cells on a large scale and may deplete normal B cells, resulting in hypogammaglobulinemia and related complications, such as infection. The length of treatment for hypogammaglobulinemia is currently inconclusive and may range from months to years, and may require a lifetime of regular treatment.

Response: IVIG treatment is proposed to restore normal serum immunoglobulin levels. The doctor should refer to the treatment plan and deal with it according to the patient's condition.

9.1.3.3 Complications of Infection

Subjects may be infected by bacteria, fungi, tuberculosis, viruses and some special microorganisms in various systems.

Countermeasures: Most of the above conditions can be alleviated by themselves or improved after symptomatic treatment, which may endanger life in rare cases. Risk prevention measures include exclusion of contraindications, strict compliance with treatment procedures and norms, close monitoring of vital signs and indicators, appropriate treatment by doctors according to the condition, symptomatic treatment.

9.1.3.4 Clinically Rare Adverse Reactions

Including acute kidney injury, cardiac arrest, left ventricular systolic dysfunction, pulmonary edema, respiratory failure, multiorgan failure, language disorder, QT interval prolongation, hypertension, hypoxia, activated partial thromboplastin time prolongation, lymphocyte count decrease, ALT increase, blood bilirubin increase, CPK increase, hyperglycemia, hyponatremia, ataxia, headache, tremor.

Countermeasures: Most of the above conditions can be alleviated by themselves or improved after symptomatic treatment, which may endanger life in rare cases. Risk prevention measures include exclusion of contraindications, strict compliance with treatment procedures and norms, close monitoring of vital signs and indicators, appropriate treatment by doctors according to the condition, symptomatic treatment.

9.1.3.5 Other Common Clinical Adverse Reactions

Include decreased neutrophil, fever, fever, hypotension, anemia, thrombocytopenia, leukopenia, elevated AST, hypokalemia, hypophosphatemia;

Countermeasures: Most of the above conditions can be alleviated by themselves or improved after symptomatic treatment, which may endanger life in rare cases. Risk prevention measures include exclusion of contraindications, strict compliance with treatment procedures and norms, close monitoring of vital signs and indicators, appropriate treatment by doctors according to the condition, symptomatic treatment.

9.2 Assessment of Adverse Events

9.2.1 Severity of Adverse Event

For each AE, the severity or change in severity was recorded at each follow-up visit. The following definitions of severity apply:

Severity	
Mild	Subject/Subject perceives signs or symptoms and tolerates them easily
Moderate	Symptoms or signs that cause discomfort and interfere with daily activities
Severe	Subject/Subject loses ability to work or perform daily activities

* Pay attention to distinguish between Seriousness and Severity of adverse events. The severity of the adverse event is defined in the Serious Adverse Event (SAE) definition.

9.3 Records of Adverse Events

9.3.1 Record of General Adverse Events

New or aggravated AEs will be recorded in the patient's source file after informed consent is signed. New or worsening AEs prior to initiation of CAR-T cell therapy (i.e., lymphodepletion) need to be recorded in the CRF if one of the following criteria is met:

- All infections
- All clinical AEs ⩾ Grade 3
- All laboratory abnormalities considered clinically significant by the investigator
- All AEs related to the study procedure
- All AEs leading to study termination

Once a patient has started lymphodepletion or the pre-infusion visit, all new or worsening AEs, including laboratory abnormalities deemed clinically significant by the investigator, will be recorded in the CRF until the 12-month visit.

AE monitoring should continue until the 24-month visit. After the 12-month visit and up to the 24-month visit, AEs need only be reported to the investigator and recorded in the CRF if one of the following criteria is met:

- The incident resulted in death
- The event is related to the study procedure
- Infection:
- Severe or opportunistic infections. Defined as a bacterial, viral, fungal or parasitic infection that meets one of the following criteria:

  A. Anti-infective treatment is required or

  B. Cause significant disability or hospitalization; or

  C. Need for surgery or other intervention
- New onset of neurological disease, or exacerbation of pre-existing neurological disease
- New onset of rheumatic or other autoimmune disease, or exacerbation of previous rheumatic or other autoimmune disease
- New onset of other hematological disease
- Any severe AE or condition that, in the opinion of the investigator, may be related to CAR-T cell therapy
- Replication capacity lentivirus (RCL) test results were positive
- Sequencing of the vector insertion site revealed mono- or oligoclonal patterns, or a location near a known human oncogene
- New malignancy (T cell & non-T cell), except primary malignancy
- Progressive multifocal leukoencephalopathy (PML)
- Hepatitis B reactivation

Whenever possible, the diagnosis should be used to describe the AE (including the laboratory abnormalities that constitute the AE) rather than individual underlying signs and symptoms. If not a definite diagnosis is identified, then each sign or symptom should be reported as a separate AE.

AEs will be evaluated according to the Medical Dictionary for Regulatory Agencies (MedDRA) and Common Terminology Criteria for Adverse Events (CTCAE Version 5.0). If no CTCAE classification exists for an AE, the severity levels of mild, moderate, severe, and life-threatening will be used, corresponding to grades 1-4. CTCAE grade 5 (resulting in death) will not be used in this study, but will be collected as a severity criterion; of course, information about the death will be collected via death form.

During screening after informed consent, and at each visit during the study, patients were interviewed non-directionally to look for the occurrence of AEs. AEs may also be detected during screening or at the

patient's initiative between visits, or by physical examination, laboratory tests, or other evaluation. To the extent possible, each AE should be evaluated to determine:

A) Severity rating (CTCAE V. 5.0, scale 1-4)

B) Duration (start and end dates)

C) Association with CAR-T cell therapy (definitely, probably, possibly, probably not, not)

D) Action taken for study or CAR-T cell therapy (none, suspended, permanently discontinued, not applicable)

E) Medication or treatment (no concomitant medication/non-medication, concomitant medication/non-medication)

F) Outcome (not recovered, recovered, recovering, recovered with sequelae, fatal, unknown)

All AEs should be treated appropriately. If concomitant medication or non-drug therapy is given, this action should be recorded in the CRF. Once identified, AEs should be followed until they are recovered or judged to be permanent, and any changes in severity, association with CAR-T cell therapy, interventions required for treatment, and outcomes should be evaluated at each visit (or more frequently, if necessary).

Progression (including a fatal outcome) of the primary study indication (i.e., the disease for which the patient was enrolled) should not be reported as an AE, but should be documented using appropriate methods.

Data Collection for Inpatient Events

Patients treated with CAR-T cells require multiple days of hospitalization and/or ICU monitoring. These AEs were mainly caused by CRS and MAS, although some may have been caused by lymphodepletion (fever with decreased neutrophil, cytopenia). CRS/MAS toxicity is an effect caused by anticipated CAR-T cell expansion, activation, and tumor cell killing.

A typical hospital or ICU may generate hundreds of data points and many therapeutic dose variations in a given day. These inpatient events and days were not scheduled protocol-defined visits, although they were expected to occur in some patients. Hospitalization data collection will be used in this study to systematically collect a subset of patient data to describe the management of safety events related to CAR-T cell therapy with the aim of:

A) Fully inform physicians and patients of the anticipated risks of CAR-T cell therapy and recommended interventions to manage these risks

B) Submitted by the Regulator

This was accomplished through targeted collection of concomitant medication and laboratory data, as well as CRFs specifically designed to capture toxicity, severity, interventions, and response/recovery to interventions associated with CAR-T cell therapy.

9.3.2 Recording and Reporting of Serious Adverse Events

Any SAE that occurred during the screening/pre-treatment phase (from the time the patient signed the informed consent form until the time the patient began investigational therapy) was only reported to the investigator and captured in the CRF and safety database if the event met at least one of the following criteria:

All events leading to death

All pulmonary or cardiac abnormalities

All infections

All events related to the study procedure

Any reportable AEs during the course of the study that also met the severity criteria

Any substantial change in the patient's status that precludes the patient from continuing CAR-T cell therapy (e.g., rapid progression of malignancy, marked decline in performance status)

Any other substantial change in the patient's clinical status, as deemed by the investigator, may have a potential impact on the patient during lymphodepletion and CAR-T cell therapy

To ensure patient safety, any SAE that occurs after the start of a patient's study-related treatment until the 12-month post-CAR-T visit, regardless of whether there is a suspected association, must be reported to the investigator within 24 hours of becoming aware of its occurrence.

Any SAEs occurring after the 12-month post-CAR-T visit and up to the 24-month visit were to be reported to the investigator and recorded in the CRF only if one of the following criteria was met:

The incident resulted in death

The event is related to the study procedure

Infection

Severe or opportunistic infections. Defined as a bacterial, viral, fungal or parasitic infection that meets one of the following criteria:

A. Anti-infective treatment is required or

B. Cause significant disability or hospitalization; or

C. Need for surgery or other intervention

New onset of neurological disease, or exacerbation of pre-existing neurological disease

New onset of rheumatic or other autoimmune disease, or exacerbation of previous rheumatic or other autoimmune disease

Emerging other hematological diseases

Any severe AE or condition that, in the opinion of the investigator, may be related to CAR-T cell therapy

RCL test results were positive.

Sequencing of the vector insertion site revealed mono- or oligoclonal patterns, or a location near a known human oncogene

New malignancy (T cell & non-T cell), except primary malignancy

PML

Hepatitis B reactivation

Any SAEs occurring after the EOT visit that the investigator suspects are related to CAR-T cell therapy need only be reported to the Yake Drug Safety Department. A recurrence, complication, or progression of the first SAE must be reported as a follow-up of the first event within 24 hours of the investigator being informed of the subsequent information. SAEs that occur at different time intervals or are otherwise considered to be completely unrelated to a previously reported event shall be reported separately as a new event.

Collect all SAE-related information and record it in the SAE report form; All applicable sections of the form must be completed to provide a clinically complete report. The investigator must assess and document the relevance of each SAE to each specific CAR-T cell treatment (if there are multiple CAR-T cell treatments), complete the SAE report form in Chinese, and submit the completed form to the investigator within 24 hours. For a description of the SAE submission process and signature requirements, please refer to the investigator folder provided to each center.

Follow-up information was submitted in the same manner as the initial SAE report. Recurrence, complications, or progression of the first event should be reported as a follow-up of the event, regardless of when it occurred. Follow-up information should describe whether the event has recovered or continued, whether and how it was treated, and whether the patient continued or withdrew from the study.

9.4 Management and Follow-Up of Adverse Events

9.4.1 Treatment of Adverse Events

If any adverse event occurs during the study, the investigator shall first judge its nature and take necessary treatment measures to deal with it, so as to maximize the protection of the rights and interests of the subjects.

9.4.2 Treatment Cost of Serious Adverse Event

For the subjects who have serious adverse events related to cell therapy, the cooperative unit shall provide legal and economic guarantees to the investigators in addition to coordinating active treatment and bearing the cost of treatment, except for those caused by medical malpractice.

9.4.3 Follow-Up of Adverse Events

The investigator shall follow up and investigate all adverse events (including serious adverse events), regularly follow up according to the patient's condition until the final outcome of the adverse events, and record the follow-up process and the outcome of the adverse events.

10 Quality Control and Quality Assurance

10.1 Monitoring Visit of the Research Center

Monitoring of this trial will be the responsibility of the investigator or the third party CRO commissioned by the investigator. The monitor will visit the study site before, during, and at the end of the study to ensure that all aspects of the protocol were adhered to. Source documents will be reviewed to verify the data recorded in the CRF. Source files are defined as original files, data, and records. The investigator and the hospital shall ensure that the collaborator or its client (CRO) and the IRB or IEC have access to the source documents.

All aspects of the study and its documentation were subject to review by the collaborator or sponsor, including, but not limited to, the investigator's folder, study medication, subject's medical records, informed consent documentation, and review of the CRF and related source documents. It is important that the investigator and other study staff be present during the inspection visit and that there be sufficient time for this work.

The purpose of monitoring is to ensure that the rights and interests of the subjects in the clinical trial are protected, the data recorded and reported in the trial are accurate and complete, and the trial complies with the approved protocol and relevant laws and regulations. The monitor shall follow the standard operating procedures and supervise the clinical trial to ensure that the clinical trial is carried out according to the protocol.

10.2 Scheme Violation

The protocol cannot be violated by the investigator unless it is necessary to eliminate an immediate hazard to the study subject. If other unforeseen circumstances arise that require changes to the protocol procedures, the investigator should consult with the collaborating or commissioning party (and the IRB or IEC, if required) to determine the appropriate course of action. Exemptions not allowed for inclusion or exclusion criteria (pre-permitted violations).

The site should document all protocol violations in the subject's source file and notify the collaborator or its client (and the IRB or IEC, if required) if a material violation occurs. Significant protocol violations include, but are not limited to, situations involving falsification or misconduct, increased risk to the health of the subject, or confusing the interpretation of the primary study evaluation. For any major violation of the protocol, the center shall fill in the protocol violation form and sign it by the partner or the client.

10.3 Quality Assurance Audit

The research center may also be subject to quality assurance audits by the partner or the client. In this case, the Partner's designated inspector will contact the Research Center in advance to schedule an inspection visit. Inspectors may request visits to the facilities where laboratory samples are collected, cells are stored and recovered, and other facilities used during the study to evaluate whether the test is conducted in accordance with the test protocol, standard operating procedures, and relevant regulatory requirements, and whether the test data are recorded in a timely, true, accurate, and complete manner.

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