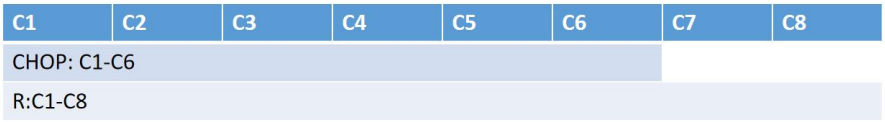
Summary of the Scheme

Sponsor: Suzhou Xinda Pharmaceutical Co., LTD	**Protocol No:** B2024-380
Study Protocol: R-CHOP	**Research stages:** stage III
Version number: 2.1	**Release date:** 2024/07/05
Popular title	High doserituxan (500 mg/m²) joint men CHOP regimen for advanced DLBCL treated first phase III clinical study.
Official title	A phase III randomized controlled trial comparing high-doserituximab (500mg/m²) plus CHOP with standard-doserituximab plus CHOP in treatment-naive men with advanced diffuse large B-cell lymphoma.
Objective	**Main Objective:** To compare the MODIFIED progression-free survival (modified-PFS) of high-dose rituximab (500mg/m²) plus CHOP versus standard-dose rituximab plus CHOP in previously untreated (TN) stage III-IV male DLBCL patients. **Secondary Objective:** To compare other efficacy indicators (EFS, OS, ORR and CRR), safety and PK characteristics of high-dose rituximab (500mg/m²) combined with CHOP regimen versus standard-dose rituximab combined with CHOP regimen in previously untreated (TN) stage III-IV male DLBCL patients
Endpoint	**Primary endpoints:** MODIFIED-PFS as assessed by an independent review Committee (IRC). **Secondary endpoints:** ORR, CRR, DOR, EFS, and OS;Adverse events and laboratory abnormalities assessed by IRC and investigator, respectively; ;EORTC QLQ-C30 and EQ-5D-5L questionnaires were used to assess the quality of life of the subjects.
Estimate the target	This study clinical problem is the main focus ofthe high doserituxan (500 mg/m²) combined CHOP scheme can improve the preious untreated (TN) of patients with stage III - IV male DLBCL MODIFIED - PFS (IRC) assessment. **Population** By randomly into group, Ann Arbor III - IV clinical stage and age < y 75 male patients with adanced DLBCL treated first. **Treatment**

	Subjects first accept for 6 cycles (21 days (d) as a treatment cycle 】 high dose (500 mg/m²) or standard dose (375 mg/m²) joint CHOP regimen for rituxan, then two cycle (21 d for a treatment cycle) high dose or standard dose of rituxan maintenance treatment. **Variables** Progression-free survival (MODIFIED-PFS), defined as the time from the date of randomization to disease progression or relapse after CR or death from any cause, whichever occurred first. **Events and treatment strategies** The treatment strategy was adopted for early discontinuation of treatment before the occurrence of MODIFIED-PFS events or change in combination therapy, that is, continue to follow up to the end of the study until disease progression or recurrence or death after CR. Patients who did not have MODIFIED-PFS events at the end of the study were treated as censored, and the censoring time was the time of the last assessment. Evaluator for baseline after there is no time, MODIFIED - PFS delete lost time as random time. For MODIFIED - PFS incidents before start a new antineoplastic therapy or use significantly affect MODIFIED - PFS ending for a drug or treatment, and so on and so forth will adopt the strategy of hypothetical variables, namely according to delete processing, delete lost time for events with time. * does not include the intrathecal injection in patients at high risk of CNS diseases prevention and involvement of the local radiotherapy for testicular lesions inpatients with testicular. **Group level summary** Hazard ratios (HRS) estimated by COX models.
Study Sites	Sun Yat-sen University Cancer Center and other research centers
Study Group	Men with advanced, treatment-naive DLBCL

Dosage regimen	The dosing regimens for the combination phase and the single-agent maintenance phase of the study are detailed in Figure 1.  **Figure 1. Dosing Regimens** **1 cycle to 6 cycles** Rituximab 500 mg/m² in the high-dose group and 375 mg/m² in the standard-dose group intravenously on day 1 (IV) (continuation the next day if needed) Cyclophosphamide: 750 mg/m², IV 1 or 2 days More gentle than star: 50 mg/m², IV 1 or 2 days Vincristine: 1.4 mg/m² IV on day 1 or 2 (maximum total dose 2 mg/ cycle) Oral prednisone: 100 mg/day, 1 to 5 days for a daily (QD) **Cycle 7 and 8 cycles** Rituxan: high dose group of 500 mg/m², the standard dose of 375 mg/m², day 1 IV (if need 2 days to complete)
Study Design	This study is a multicenter, randomized controlled phase III clinical study, Main evaluation high-dose rituxan (500 mg/m²) in combination with CHOP plan comparison standard dose rituxan combined CHOP scheme in preious untreated (TN) in male patients with DLBCL MODIFIED improved progression-free surial (MODIFIED - PFS). Before the start of the signed written informed consent and randomization, all participants shall provide sufficient tumor tissue biopsy samples for central laboratory by HE staining and IHC testing identified as DLBCL patients. Eligible subjects according to the proportion of 1:1 were randomly into the experimental group (rituxan 500 mg/m²) or control group (rituxan 375 mg/m²), participants will receive 6 cycles R - CHOP treatment (21 d for a cycle), and the subsequent 2 cycle lastsrituxan treatment (21 d for a cycle). No crossover between the two groups was performed during the study. The overall study design is detailed in Figure 2

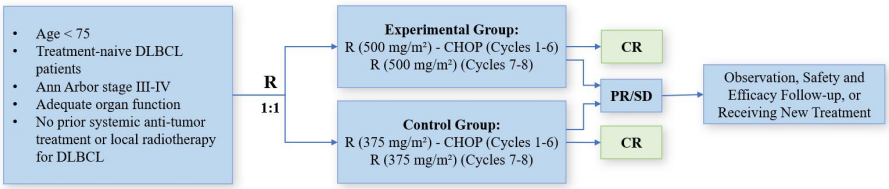


Figure 2. The overall design

Research Process

1) Screening period/baseline period (-28 days to -1 day)

Participants will experience less than 28 days before randomization screening period, as shown in the flow chart of research 2. Confirmed by the researchers in accordance with the inclusion criteria and do not accord with standard of exclusion, participants will be randomly assigned to the experimental group according to the ratio of 1:1 (rituxan 500 mg/m^2) or control group (rituxan 375 mg/m^2).

Subjects should be in the 24 hours after randomization to research therapy (if there are special circumstances should communicate with bidders in advance).

Common adverse reactions of prevention:

1) Tumor lysis syndrome (TLS) : Exist for risk factors of subjects, including high tumor burden, lymph, lactate dehydrogenase (LDH) higher than the upper limit of normal (ULN) 2 times, dissolve the spontaneous tumor syndrome, peripheral blood lymphocyte count absolutely obvious rise, disease significantly affects the bone marrow, high uric acid hematic disease history, don't Piao alcohol treatment is invalid and kidney function not entire, It is recommended that TLS prevention measures, including hydration, urate-lowering medication, and correction/monitoring of serum uric acid, creatinine, and electrolytes, should be given before the initiation of treatment.

2) Reactivation of hepatitis virus: For subjects who are HBsAg positive or HBcAb positive and HBV-DNA negative at screening, HBV-DNA levels should be monitored regularly during the trial and preventive antiviral therapy (such asentecavir or tenofovir) should be given. Suggest preventive antiviral treatment until the end of the study medication after 6 to 12 months or rituxan treatment at least 18 months after the end (shall be subject to late), specific Suggestions under the guidance of specialized subject doctor treatment and follow-up. Participants who were positive for hepatitis C virus antibody (HCV) and negative for HCV-RNA at screening were required to have continuous monitoring of HCV-RNA levels during the course of the trial if they had not received systemic anti-HCV therapy.

	2) treatment (combination, a total of 6 cycles, two separate cycle rituxan maintenance treatment, every 21 days for a cycle) This stage study of supervision and inspection process can be found in the flow chart of research (phase III), and subsequent adjustments may according to the condition of the preliminary data and execute. This study is not allowed to cross the treatment group. **3) early withdrawal from treatment/end of treatment (EOT) visit** If subsequent participants will no longer accept treatment, the test program should be as soon as possible after participants stopped test drugs/treatment (combination during the proposal in the exit / 7 to 14 days after the end of treatment, single drug maintenance phase Suggestions in the last 7 days) after the treatment of EOT visit evaluation, Including a complete physical examination, ECG, ECOG score, vital signs, weight, adverse events and drug combination information collection, recycling agents and participants log card, laboratory examination, electrocardiogram (ECG), serum pregnancy test (female) with fertility potential safety evaluation and curative effect evaluation (if applicable). If a participant discontinued treatment for toxicity or other reasons at a visit and did not subsequently continue protocol-specified treatment, that visit was considered to be an EOT visit. **4) after the follow-up treatment** **Security: follow-up** after the subjects complete solution treatment or exit, must record all AE and drug combination to 28 days after the last delivery or start a new antineoplastic therapy before (before), unless some subjects refused, death, lost to follow-up or withdraw his knowledge, and so on and so forth. The safety visit could not be repeated if it occurred within 7 days of the EOT visit. All preexisting or new-onset AEs or SAEs within 28 days of the last dose were followed until resolved, stabilized, or returned to baseline, unless they were considered by the investigator to be unlikely to resolve because of the patient's illness. **The effectiveness and survival follow-up:** After the subjects complete solution treatment or exit, for disease has not been progress of subjects, to recommend to evaluate tumor (1 year for every 12 weeks (plus or minus 7 days) for a, 2-5 years of every 24 weeks (+ / - 14 days) once, only when the clinical indications for 5 years later). However, safety assessment was not performed (provided that the post-treatment safety follow-up had been completed and there were no AEs or SAEs considered by the investigator

<table>
<tr><td></td><td>to be required for follow-up). In the event of disease progression or start using systemic antitumor drugs or other treatments, is as far as possible before starting the new antineoplastic therapy of tumor assessment conducted within 60 days (curative effect evaluation can avoid), to evaluate tumor will no longer follow-up, each 12 weeks after (plus or minus 7 days) to a telephone follow-up, Survival calls were performed every 12 weeks (± 7 days) thereafter to obtain data on overall survival and the use of antineoplastic therapy after the study until death, refusal to follow up, or loss to follow-up.</td></tr>
<tr><td>Randomization (applicable to the phase III studies)</td><td>Don't repeat hierarchical block random methods, by the proportion of 1:1 randomly generated by a blind statisticians subjects treatment allocation code (random table). The randomization table was then uploaded to the central randomization system for systematic configuration. The subjects' eligibility once confirmed, by the researchers on the central randomization system, input subjects after the relevant information of the participants random number and the number of drug, researchers according to drug number give corresponding treatment. Subjects will be in accordance with the proportion of 1:1 were randomly into the experimental group (rituxan 500 mg/m²) or control group (rituxan 375 mg/m²), participants will receive 6 cycles R - CHOP treatment (21 d for a cycle) after 2 cyclesrituxan maintenance therapy (21 d for a cycle).</td></tr>
<tr><td>Blinded</td><td>This study was an open randomized controlled clinical trial. Subjects and researchers have known group of experimental group and the control group, as well as for intervention measures.</td></tr>
<tr><td>The Study Drug Usage and Dosage</td><td>1) R - CHOP[1]: 1-6 cycles
<table>
<tr><th rowspan="2">Drug name</th><th rowspan="2">Dosa\ge</th><th rowspan="2">Usage</th><th colspan="3">Duration of medication</th></tr>
<tr><th>Day 1</th><th>2-5 days</th><th>Days 6-21</th></tr>
<tr><td>Rituximab</td><td>375 mg/m²
500mg/m²</td><td>IV</td><td>X[2]</td><td>No medication</td><td>Not giving medication</td></tr>
<tr><td>Cyclophosphamide</td><td>750 mg/m²</td><td>IV</td><td>X[2]</td><td>No medication</td><td>Not giving medication</td></tr>
<tr><td>Doxorubicin</td><td>50 mg/m²</td><td>IV</td><td>X[2]</td><td>No medication</td><td>Not giving medication</td></tr>
<tr><td>Vincristine</td><td>1.4 mg/m²</td><td>IV (Maximum total dose 2 mg/ cycle)</td><td>X[2]</td><td>No medication</td><td>Not giving medication</td></tr>
<tr><td>prednisone</td><td>100 mg/ day</td><td>PO</td><td>X</td><td>X (daily)</td><td>No medication</td></tr>
<tr><td colspan="6">IV: Intravenous administration; PO: oral medicine</td></tr>
</table>
Note[1]: each cycle 1 (or 2) days of R - CHOP components dosing sequence is as follows: first of all to prednisone, followed by rituxan. Subsequent</td></tr>
</table>

<table>
<tr><td></td><td>infusions of cyclophosphamide, vincristine, and doxorubicin were administered according to site clinical practice and guideline recommendations.
Note[2]: R - CHOP plan will be a total treatment for 6 cycles (21) days for a cycle, R - CHOP of drugs (rituxan, cyclophosphamide, more gentle than the star and vincristine) allow within two days to complete, cyclophosphamide, more gentle than the star and vincristine can also be used in each cycle, the second day of drug use.
Note[3]: if used before C1D1 cyclophosphamide reduced tumor, C1 can only use the remaining doses of cyclophosphamide.
2) rituxan (R)[4] : 7-8 cycles
<table>
<tr><th rowspan="2">Drug name</th><th rowspan="2">Dosage</th><th rowspan="2">Usage</th><th colspan="3">Duration of medication</th></tr>
<tr><th>Day 1</th><th>2-5 days</th><th>Days 6-21</th></tr>
<tr><td>Rituximab</td><td>375 mg/m2
500mg/m2</td><td>IV</td><td>X</td><td>No medication</td><td>Not giving medication</td></tr>
<tr><td colspan="6">IV: Intravenous administration</td></tr>
</table>
Note[4]: A dose of ⩽10mg of dexamethasone or equivalent glucocorticoids was allowed to prevent adverse effects before the administration of R (excess use in special cases was determined after discussion between the investigator and the sponsor). Rituximab was allowed to be completed on 2 consecutive days.</td></tr>
<tr><td>Principles of Dose Adjustment</td><td>Recommendations for drug dose adjustments in the R-CHOP regimen (refer to the package insert for details) :
Rituximab: the dose of rituximab was 500 mg/m² BSA (body surface area) in the high-dose group and 375mg/m² in the standard-dose group, and dose reduction was not recommended. For any level 4 adverse events or any associated with rituxan (sure about, is likely to be relevant, may) and the clinical significance of grade 3 adverse events, and should delay rituxan, until the return to baseline or completely back to normal. To prevent infusion reactions or infusion reaction processing details see the latest instructions.
Participants who discontinue rituximab treatment should discontinue participation in the study.
Cyclophosphamide: cyclophosphamide dose adjustment should follow the instructions. The most commonly reported adverse effects of cyclophosphamide are hematologic toxicities (e.g., leukopenia, anemia, and thrombocytopenia). Cyclophosphamide therapy may occur after hemorrhagic cystitis and blood in the urine, may need to stop to medicine. Prophylactic treatment for hemorrhagic cystitis was administered according</td></tr>
</table>

to the manufacturer's instructions and according to center routine.

If a participant's blood count did not meet the parameters of the general principles, treatment with cyclophosphamide and doxorubicin was delayed. Appear when the subjects thought associated with cyclophosphamide and more gentle than stars hematology toxicity, suggested the next cycle day 1 adjustment in accordance with table 2 dose cyclophosphamide and more gentle than the stars.

Table 1. Recommendations for dose Adjustments for cyclophosphamide - or doxorubicin-Related Hematologic toxicity

Neutrophil count	Platelet count	Give the dose (later period)
Acuity 1.0 x 10^9 / L	≥75× 10^9/L	Dose unchanged
Acuity 0.5 x 10^9 / L, without febrile neutrophilic reduce disease *	≥50× 10^9/L	The neutrophilic granulocyte count in return to acuity 1.5 x 10^9 / L and platelet recovery after 75 x 10 /^{9} L or higher, dose the same
< 0.5 x 10^9 / L and/or febrile neutrophilic reduce disease (unused growth factor)	/	Start with the support of growth factors continue to medicine, dose the same
<0.5×10^9/L and/or febrile neutropenia (despite the use of growth factors), first occurred	<50× 10^9/L (first occurrence)	25% dose reduction
Second occurrence	<50× 10^9/L (second occurrence)	Decrease the dose by another 25%
A third occurrence	< 50 x 10^9 / L (the third)	Permanent discontinuation of medication

Note: ANC = absolute neutrophil count

* febrile neutrophilic reduce disease is defined as the ANC < 0.5 x 10^9 / L or expected to 48 hours after the ANC < 0.5 x 10^9 / L, and single oral temperature 38.3 ℃ or higher (axillary temperature is 38.0 ℃ or higher), or oral temperature 38.0 ℃ or higher (axillary temperature is 37.7 ℃ or higher) that persists for more than 1 hour.

Doxorubicin: Dose adjustment of doxorubicin should follow the instructions. More gentle than the biggest star cumulative dose limit for 450 to 550 mg/m^2. The maximum cumulative dose administered to each subject in this study was 300 mg/m^2. Dose-limiting toxicities of doxorubicin therapy include myelosuppression, cardiac toxicity, and gastrointestinal

effects such as mucositis. Bone marrow inhibition usually demand reached a low point in the 10 to 14 days after treatment, more gentle than star hematology toxicity dosage adjustment suggestion see table 2. Cardiac toxicity can occur at directly after the treatment, may also be in weeks or months after the treatment or continued. More gentle than star hepatic metabolism, and with the bile excretion. Impaired liver function results in slower excretion of the drug, which in turn results in increased drug toxicity. If liver function is damaged, it is suggested that in accordance with table 3 more gentle than star dose adjustment. Dose adjustments are not required in subjects with Gilbert's syndrome and in cases in which elevated bilirubin is due to nonhepatic causes.

Table 2. Dose Modifications of Doxorubicin for Hyperbilirubinemia

Serum total bilirubin level	Dose adjustment measures
2.0 3.0 mg/dL, or 34.2 51.3 mu mol/L	50% of the normal dose
> 3.0 mg/dL, or 51.3 mu > mol/L	25% of the normal dose

Vincristine, vincristine dose adjustment should follow the instructions. If the dose of vincristine is impaired based on liver function, then the dose of vincristine should be adjusted according to Table 4. When hyperbilirubinemia improves, the vincristine dose can be escalated again. For subjects and elevated bilirubin gilbert syndrome, due to the liver causes do not require dose adjustment.

Table 3. Vincristine Dose Modifications for Hyperbilirubinemia

Serum total bilirubin level	Dose adjustment measures
2.0 3.0 mg/dL, or 34.2 51.3 mu mol/L	75% of the normal dose
>3.0 mg/dL or 51.3 μmol/L	50% of the normal dose

In addition, the vincristine nervous system toxicity are most frequently reported adverse reactions, related with dose and age. Vincristine should be withheld in case of grade 3 neurotoxicity, especially if paresthesia or signs of paresis are present. After resolution of symptoms, vincristine could be resumed at 50% of the original dose. For any type of grade 4 neuropathy, shall be permanently disabled vincristine. For any episode of intestinal obstruction/constipation requiring hospitalization, the vincristine dose should be reduced by 25% when the drug is resumed.

Prednisone: Dose adjustments of prednisone should follow the

	instructions. High-dose prednisone or equivalent for the subjects some adverse situation in the aftermath of the drugs (e.g., bacterial infection, viral infection, systemic fungal disease, high blood pressure, diabetes and gastrointestinal adverse conditions, such as peptic ulcer, pancreatitis and diverticulitis) or relatively high risk of adverse conditions is aggravating, deal with the subjects are closely monitored. If participants in the adverse reactions associated with prednisone, and intolerance to research plan calls for dose (100 mg/day), can be appropriately adjust the dose of prednisone, but should be not less than 80 mg/day. In some special cases, the subjects could not tolerate prednisone in the treatment of sudden discontinuation in 5 days. In such cases, it may be necessary to taper the dose to withdrawal.
Pharmacokinetic Study	A total of PK blood samples were planned to be collected from approximately 150 subjects in the experimental and control groups. PK blood samples were collected within 1h before administration and 2h to 6h after administration. According to the research process in each plan blood sampling time point to 3 ml of whole blood to collect blood vessels, according to the biological analysis method development situation, according to the related SOP for handling, storage and transportation of blood samples.
Inclusion Criteria	1, age < 75 y, male patients; 2. According to the 2017 revised WHO classification criteria, the subject was diagnosed with DLBCL; 3.On the basis of Ann Arbor staging for stage III - IV patients; 4. No previous anti-tumor systemic therapy or local radiation therapy for DLBCL (except previous cytoreductive therapy such as glucocorticoids and intrathecal CNS prophylaxis) 5.Expected survival of≥6 months. 6.the participants need to have enough blood coagulation function and liver and kidney function, local laboratory tests need to meet the following criteria: A. blood coagulation function: prothrombin time (PT) and part of the blood coagulation time (APTT) live enzymes acuities were 1.5 times the upper limit of normal (ULN); B. the liver: without clear liver involvement, nmda aminotransferase (AST) and alanine aminotransferase (ALT) or less 3.0 x ULN, serum total bilirubin 1.5 x ULN or less; If you have liver involvement, AST and ALT acuities were 5.0 x ULN, total bilirubin 3.0 x ULN or less; If

	there is a clear Gilbert syndrome (non combined with high blood bilirubin), total bilirubin 3.0 x ULN or less; C. kidney: serum creatinine (Scr) 1.5 x ULN or less, or creatinine clearance rate (Ccr) or greater 50 ml/min (according to CockcroftGault formula or use 24 hours urine test). When the unit of serum creatinine as mg/dL: $$\mathrm{Ccr} = \frac{(140 - \text{年龄}) \times \text{体重(kg)} \times [1.0, \text{男性}; 0.85, \text{女性}]}{72 \times \text{血清肌酐 (mg/dL)}}$$ When the basic unit of serum creatinine is mu mol/L: $$\mathrm{Ccr} = \frac{(140 - \text{年龄}) \times \text{体重(kg)} \times [1.0, \text{男性}; 0.85, \text{女性}]}{0.818 \times \text{血清肌酐 (μmol/L)}}$$ 7.the subjects have enough bone marrow function, drug use (or random) laboratory hematology inspection before must meet the following criteria: A. neutrophil count (ANC) absolutely acuity 1.5 x 109 / L, in the case of disease involving the bone marrow allows the use of growth factors (after discussing with the sponsor decided required) to stimulate the ANC to achieve the above standard B. 75 x 109 / L or higher platelet (don't lose platelets within 5 days before the screening, allows the use of TPO growth factors such as support to the standard) C. if disease involving autoimmune hemolytic anemia caused by bone marrow or lymphoma, hemoglobin acuity 8.0 g/dL (80 g/L); A hemoglobin level of 9.0 g per deciliter (90g per liter) or higher if the disease does not involve the bone marrow (no red-cell transfusion within 7 days before screening; Allows the use of growth factors such as EPO support to achieve the standard). 8.All patients should use medically approved contraception for 12 months after rituximab administration (according to the marketed package insert, as appropriate). 9. Participants voluntarily enrolled in the study and provided written informed consent to follow the trial regimen and visit schedule.
Exclusion Criteria	1.The researchers assessed as intolerance to R - CHOP plan and/or subjects of any drug treatment; 2.Received any previous anti-lymphoma systemic therapy or local radiation therapy. Note: always short-term [such as the duration of 10 days or less] glucocorticoid (100 mg/day or less prednisone or equivalent drugs) used for decreasing tumor treatment and prevention of its sheath (CNS) does not

	belong to the definition of lymphoma systemic treatment. 3.Consider lymphoma involving the central nervous system (CNS) of patients or a diagnosis of primary central nervous system lymphoma (PCNSL). The patient was diagnosed with primary mediastinal large B-cell lymphoma (PMBL). 4.Previous organ transplantation or hematopoietic stem cell transplantation; Planned during the study period accept allogeneic hematopoietic stem cell transplantation (allo - HSCT) or autologous hematopoietic stem cell transplantation (auto - HSCT). 5.For the first time use (or random) before 4 weeks before received or during the study period or major injury, is expected to undergo a major operation in 4 weeks of antineoplastic drugs or medical devices clinical trials; For the first time within 14 days (or random) before using this drug treated with warfarin or other vitamin K antagonists, 5 days received potent and of CYP3A4 inhibitors or within 3 days to eat grapefruit, carambola, Serbia, orange, grapefruit and grapefruit juice. 6.Has in the past three years with other malignant tumor except this study target indication, but after radical treatment to cure skin basal cell carcinoma, cervical carcinoma in situ, squamous cell carcinoma of the breast carcinoma in situ, limitations, and received radical surgery, the researchers determined have been cured except other malignant tumors. 7.Any serious and/or failing to control systemic disease, the researchers determine doesn't fit in the subjects of this study (including the activity of CTCAE level 2 or more clinical severe infection, drug can not control of high blood pressure, diabetes, unstable angina pectoris, congestive heart failure, the need for oxygen respiratory system disease, severe vascular embolization, Uncontrollable bleeding or important internal bleeding, severe liver and kidney or metabolic diseases, such as phase decompensated cirrhosis of the liver, kidney failure, etc.). 8.For the first time (or random) before using this drug had significant cardiovascular disease within six months, if you have symptoms of arrhythmia, myocardial infarction, stroke, history of intracranial hemorrhage. Poor heart function, including the conform to the New York heart association (NYHA) cardiac function classification level 2 or higher, in three separate or shown on the electrocardiogram (ecg) correction of Fridericia formula of QTc (QTcF) greater than 480 ms or echocardiographic examination showed left ventricular ejection fraction

	(LVEF) < 50%. Note: NYHA heart function classification 2 levels of physical activity is defined as a mild restrictive, resting not self-conscious symptom, physical activity to cause excessive fatigue, heart palpitations, asthma, or angina pectoris; QTcF was calculated by QT/[RR^0.33], where RR=60/ heart rate. 9. Disease states with clinical manifestations that may be difficult to control, including but not limited to: • Human immunodeficiency virus (HIV) infection, syphilis infection, HBsAg or HBcAb positive and HBV - DNA test results above research center, detection limit, HCV antibody positive and HCV - RNA detection threshold test results above research center; • Uncontrolled systemic active bacterial, fungal, or viral infection and active tuberculosis infection. 10. Any impact on patients with swallow medications, and seriously affect the test drug absorption orpharmacokinetic parameters, including difficult to control such as nausea and vomiting, short bowel syndrome. 11. In the study period can't interrupt taking/strong CYP3A inhibitors and inducers, OATP1B1 / OATP1B3 sensitive substrates. 12. The first time (or random) before 4 weeks before using this drug or treatment plan during the study or research accept live vaccine or within 4 weeks after the end of live attenuated subjects. 13. The presence of A bleeding disorder (such as von Willebrand disease or hemophilia A, hemophilia B, etc.) or a definite bleeding tendency according to the investigator's judgment. 14. Patients with severe peripheral or central nervous system disease, such as a history of progressive multifocal leukoencephalopathy or ongoing confirmed progressive multifocal leukoencephalopathy. 15. During the study period need to use warfarin or other vitamin K antagonists. Note: Low-dose aspirin, low-molecular-weight heparin sodium were allowed; Allow new oral clotting factor Xa antagonists (such as pp shaaban, according to the degree of sand sand and cut class). 16. Autoimmune disease (other than immune thrombocytopenia due to lymphoma or autoimmune hemolytic anemia) that could not be controlled or required treatment within 4 weeks before the first dose of medication (or before randomization) . 17. Prior exposure to ≥150 mg/m^2 doxorubicin ($^{\text{or other}}$ anthracyclines converted according to cumulative cardiac toxicity).

	18. Researchers think that there are not suitable for participants to participate in the test of other conditions.
During the study period allows the combination of medication and therapy	In does not affect the research objective to observe the situation, the subjects during the study period acceptable reasonable best support treatment, including hematopoietic growth factors, blood transfusion or blood products (such as transfusion of red blood cells and platelets), body fluids and electrolytes supplement and appropriate antibiotic therapy, etc. In order to reduce neutrophil reduce the risk of infection, unless the taboo or intolerance, otherwise all into the group of subjects require the use of granulocyte colony stimulating factor (g-csf) as a primary prevention, and in the subsequent chemotherapy cycle duration. This study allows the rituxan (R) drug delivery before the use of acetaminophen, diphenhydramine (or other appropriate antihistamines) front of drugs, and 10 mg or less dexamethasone or equivalent glucocorticoid to prevent infusion reactions associated with R (special cases need excessive use, subject to the researchers decided after discussing with the sponsor). To allow participants in this study R - CHOP plan dosing and R to study outside of medicine before using 20 mg/day or less during the period of treatment prednisone (or equivalent), used for lymphoma symptoms control other than the purpose. Allows use of corticosteroids in the first drug (up to 100 mg/day of prednisone or equivalent drug) to control the tumor, lymphoma symptoms or minus 10 days the longest can continue to use (such as excess or in excess of the prescribed time, need to communicate with the sponsor of medicine), but it's important to note that disease stages must be completed before the start of the glucocorticoid treatment. Only in R - CHOP research plan during the treatment, allows the use of proton pump inhibitors, each period the longest use 5 days. Drugs to prevent the development of TLS and reactivation of HBV. Allow the cartesian pneumocystis pneumonia according to the clinical routine preventive treatment. Patients with CNS high risk factors (CNS-IPI score of 4 or higher) were allowed CNS prophylaxis (e.g., triple intrathecal cytidine, methotrexate, and dexamethasone) during the study. Allow to testicular diseases involving patients with testicular lesions radiotherapy.

Medications and treatments that were not allowed during the study	• Any investigational medication; • Anti-tumor drugs for any indication other than the study protocol, including Chinese herbal medicine; • Any antineoplastic treatment, including surgery, local radiotherapy (except for patients with disease involving the testes), and stem cell transplantation; • Live or attenuated live vaccines; • Warfarin or other vitamin K antagonists.
Criteria for subjects to discontinue treatment	1. Patients or their legal representatives request to withdraw from the study, such as patients who cannot tolerate AEs and request to withdraw from the study treatment; 2. The investigator decided that the study treatment should be terminated based on the best interests of the patients; 3. There is evidence of disease progression or recurrence, or the efficacy is evaluated as SD after the completion of combination therapy; 4. Complete the prescribed cycle of treatment; 5, the researcher and/or the sponsor considers the patient compliance; 6. The use of other anti-tumor therapies, such as stem cell transplantation; 7. Patient loss to follow-up [failure to contact the subject or family member after a minimum of 3 documented telephone calls or emails on different calendar days within 1 month]; 8. The patient died.
Study period	The projected duration of the study was 7 years. Participants could receive the study drug and regimen until they had disease progression or relapse or unacceptable toxicity, whichever occurred first, after completing the prescribed cycles.
Safety Assessment	All subjects receiving the drug will be evaluated for safety. Safety was evaluated by means of vital signs, physical examination, laboratory testing, electrocardiography, and reporting of adverse events and serious adverse events. Safety was followed up until 28 days after the completion of the protocol or withdrawal from the study.
Evaluation OF Efficacy	The efficacy was evaluated according to the 2014 version of the Lugano criteria for non-Hodgkin's lymphoma (NHL) (Cheson, BD et al. 2014), as described in Appendix 3.

Statistical Methods	**Statistical Analysis set** Full analysis set (FAS) : All cases were included as much as possible based on the intention-to-treat (ITT) principle. The definition ofFAS for this study was consistent with that of the population in the primary estimation objective: male, previously untreated patients with DLBCL who had undergone randomization and received at least one dose of a study drug were eligible for FAS. Per-protocol set (PPS) : subjects in the full analysis set who had good treatment adherence (70%-120%), no major protocol violations, and available primary endpoint. PPS will be used for supplementary analysis of efficacy. Safety data set (SS) : used at least once included in all test drugs, and drug safety data recorded after the subjects. Pharmacokinetic analysis set (PKS) : All subjects who received at least one dose of trial drug, had pharmacokinetic data (biological samples were collected), and no major protocol violations were included. Exploratory study analysis set: Subjects with exploratory study data and no major protocol violations in the FAS set were included. **Safety ANALYSES** Safety data sets were used for safety analysis. The descriptive statistics and summary of adverse events occurred in the experimental group and control group, all the adverse events (AE), level 3 and above AE, adverse events related to study drug (TRAE), level 3 and above TRAE, Serious adverse event (SAE), related to study drug SAE (SAR), led to the drug suspension, dose adjustment or permanent discontinuation ofAE and pay special attention to adverse events (AESI) will be according to the organ systems, the preferred term and category summary of cases, the number of cases, and the incidence. Trends in laboratory tests, vital signs, ECOG performance status, and electrocardiographic measurements will be explored and summarized or compared with baseline if necessary. **Efficacy ANALYSIS** Primary estimation analysis and sensitivity analysis were performed based on FAS, and PPS was used as supplementary analysis. MODIFIED-PFS was defined as the time from the date of randomization to receipt of second-line therapy, first documented recurrence, or progression. Between-group differences in MODIFIED-PFS were analyzed using the stratified Log-rank test, with the same stratification factors as those used at randomization. Use the Kaplan - Meier (KM) method to estimate the

	MODIFIED - PFS curve of each team, a MODIFIED - PFS and 3 years in MODIFIED - PFS rate, The 95% confidence interval for median modify-PFS was estimated by the Brookmeyer-Crowley method, which used the log-log function transformation to achieve normal approximation. MODIFIED - PFS risk ratio (HR) and 95% confidence interval, the use of the stratified Cox proportional hazards models to estimate, layered with stratified random factors. In addition, considering the possibility of informative censoring of the censored data, the control-based multiple imputation method will be considered for sensitivity analysis after processing the censored data. Details of the methods are provided in the statistical analysis plan. Other efficacy indicators included EFS, ORR, CRR, DOR, OS, etc. Defined EFS: for the first time to give medicine to disease progression or recurrence after CR, cannot stop drug tolerance toxicity of lead to permanent, start the anti-tumor treatment or death from any cause (with whichever) happen first time. Patients without EFS events at the time of analysis were censored according to the time point of the last evaluation. ORR: ORR is defined as a percentage of all cases of CR and PR cases. CRR: is defined as a percentage of all cases of CR cases. DOR (for all subjects achieving response) : Defined as the time from the first assessment of response to the first assessment of disease progression or relapse or death from any cause. OS: defined as time from first dose to death from any cause. Persons free from death at the time of analysis were censored at the date they were last known to be alive. ORR between treatment group and comparison CRR adopts hierarchical Cochran Mantel Haenszel compared between groups (CMH) method, and calculate the difference between groups rate 95% CI of reduction of the control group (test group), layered with stratified random factors. At the sametime, the Logistic model was fitted to calculate the ORR, CRR and 95% confidence interval of each treatment group with and without stratification factors, and the difference of ORR and CRR and 95% confidence interval between the two groups, respectively. The analysis methods of DOR, EFS and OS were the same as MODIFIED-PFS. In addition, for subjects without documented end-point events before the data cutoff and those who did not fully follow the tumor evaluation procedure, different specific censoring rules will be formulated, and sensitivity analyses will be provided for different censoring treatments.

	Pharmacokinetic study: the drug concentration-time data of each subject were calculated, the concentration-time curve was drawn, and the average blood concentration - time curve was drawn. The pharmacokinetic parameters were also calculated after drug administration. Based on the previously obtained pharmacokinetic characteristics and models, the population pharmacokinetic characteristics of the study subjects were established, and the effects of concomitant medications and disease/physiological factors on the pharmacokinetic characteristics of rituximab were evaluated.
Sample Size	The final enrollment will include all patients for whom data on safety, tolerability,pharmacokinetics, and efficacy were available during the combined study.
Independent data Monitoring Committee (IDMC)	The IDMC (composed of senior clinical experts with relevant disease expertise and clinical trial statistics experts) was established before the entry of the key registration clinical study. The IDMC was mainly responsible for regularly reviewing the accumulated data of this clinical trial to protect the safety of subjects, ensure the reliability of the trial, and ensure the validity of the trial results. The specific content will be elaborated in the charter of IDMC.
Study Protocol Modifications	Modifications to the protocol will be made as necessary based on available human pharmacokinetic parameters, safety, tolerability, and preliminary efficacy data. All amendments to the protocol had to be approved by the sponsor, the investigators, and the ethics committee.