Supplementary Online Content

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Supplement. Trial Protocol of the Parent Study

This supplementary material has been provided by the authors to give readers additional information about their work.

A prospective, multicenter randomized phase III clinical trial of intensified chemotherapy in improving the treatment efficacy of patient with diffuse large B-cell lymphoma

Applicant institution: Sun Yat-Sen University Cancer Center

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Version: 2.0

Date: 20110113

Remark: the primary version of this protocol was in Chinese. We have translated it into English.

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List Of Abbreviations

ADCC	**Antibody-Dependent Cell-mediated Cytotoxicity**
AE	**Adverse Event**
ALT	**Alanine aminotransferase**
AST	**Aspartate aminotransferase**
CDCC	**Complement-Dependent Cytotoxicity**
CHOP	**Cyclophosphamide, Doxorubicin, Vincristine, Prednisone**
CHOP-14	**CHOP given every 2 weeks**
CHOP-21	**CHOP given every 3 weeks**
CR	**Complete Remission**
CRR	**Complete Remission Rate**
CRF	**Case Report Form**
CT	**Computerized Tomography**
CTCAE	**Common Terminology Criteria for Adverse Events**
DFS	**Disease Free Survival**
DLBCL	**Diffuse Large B-cell Lymphoma**
ECOG	**Eastern Cooperative Oncology Group**
GCP	**Good Clinical Practice**
IPI	**International Prognostic Index**
ITT	**Intent-To-Treat**
G-CSF	**Granulocyte Colony-Stimulating Factor**
MRI	**Magnatic Resonance Imaging**
NCCN	**National Comprehensive Cancer Network**
NCI	**National Cancer Institute**
NHL	**Non-Hodgkin Lymphoma**

OS	**Overall Survival**
ORR	**Overall Response Rate**
PD	**Progressive Disease**
PP	**Per Protocol**
PR	**Partial Remission**
R-CHOP	**Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone**
R-CHOP-14	**R-CHOP given every 2 weeks**
R-CHOP-21	**R-CHOP given every 3 weeks**
SAE	**Serious Adverse Event**
SD	**Stable Disease**

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Protocol Summary

Applicant	Sun Yat-Sen University Cancer Center
Phase	Phase III
Indication	Newly diagnosed diffuse large B-cell lymphoma
Objectives	Compare 5-year DFS rate between R-CHOP-21 group and R-CHOP-14 group; Compare ORR, CRR, OS and safety between the two groups.
Study design	prospective, multi-center, parallel, controlled, open-label, randomized phase Ⅲ study
Subjects required	454 subjects
Study sites	10 study sites (Sun Yat-Sen University Cancer Center, The First Affiliated Hospital of Sun Yat-sen University, The Third Affiliated Hospital of Sun Yat-sen University, The Fifth Affiliated Hospital of Sun Yat-sen University, Beijing Cancer Hospital, Southern Hospital of Southern Medical University, The First People's Hospital of Foshan, People's Hospital of Zhongshan, Shantou University Medical College and Kiang Wu Hospital)
Screening Criteria	Newly diagnosed DLBCL adult subjects without treatment contraindication
Study duration	The enrolment of the study will start from January, 2011 and end at December, 2018
Control Group	R-CHOP given every 3 weeks for a total of 3-8 cycles
Experimental Group	R-CHOP given every 2 weeks for a total of 3-8 cycles
Primary endpoint	5-year disease free survival (DFS)
Secondary endpoints	ORR, CRR, OS and safety
Study procedures	This is a prospective, multi-center, parallel, controlled, open-label, randomized phase Ⅲ study. A total of 454 subjects with newly diagnosed diffuse large B-cell lymphoma meeting the inclusion criteria is required. After giving written informed consent, all subjects will be randomized to R-CHOP-21 group or R-CHOP-14 group Subjects will receive safety assessments after every cycle of chemotherapy and efficacy assessments after every two cycles of chemotherapy. Follow-up period starts after the completion of chemotherapy and follow-up visits will be performed every three months.

Statistical Analysis	454 subjects with newly diagnosed DLBCL will be randomized to two groups at a 1:1 scheme. The ORR and CRR will be compared between the two groups on ITT and PP population. All AEs of the study will be analyzed.

1. Background

There are several known prognostic factors for non-Hodgkin lymphoma (NHL). Besides histologic subtype, the prognosis of NHL is mainly related to clinical characteristics such as International Prognostic Index (IPI), which is also suitable for predicting the outcome of Chinese patients with diffuse large B-cell lymphoma (DLBCL) and distinguishing high-risk patients with poor response to conventional chemotherapy. In pre-rituximab era, the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen given every 3 weeks (CHOP-21) was standard care for aggressive NHL. On the basis of the high proliferation rate of tumor cells in patients with aggressive NHL and the significant maturity of blast neutrophile granulocytes stimulated by granulocyte colony-stimulating factor (G-CSF) in preclinical studies, we have reduced treatment intervals from 3 to 2 weeks (CHOP-14) with prophylactic use of G-CSF and demonstrated that CHOP-14 significantly improved 5-year disease-free-survival rate compared to standard CHOP-21 (31.46% vs. 12.5%) in randomized study in high-risk DLBCL patients. Similar findings were reported in recent studies performed in America, Japan and Europe. Concurrent with the result, the dose-intense regimen CHOP-14 also improved outcome of DLBCL patients with low IPI.

Rituximab, a human-mouse chimeric monoclonal antibody that binds specifically to the CD20 antigen located on B lymphocytes, can induce CD20-positive B-cell depletion as a result of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDCC). During the period from 2003 to 2005, several international, multi-center, randomized clinical trials have confirmed that rituximab in combination with CHOP-21 (R-CHOP-21) significantly improved response rate and overall survival compared to CHOP-21 alone in DLBCL patients without additional serious toxicity. Similar results were achieved in Chinese patients. Consequently, both CHOP-14 and R-CHOP-21 have been the most outstanding advances in the treatment of DLBCL recently.

Both CHOP-14 and R-CHOP-21 improved outcome of DLBCL. However, whether rituximab

combined with CHOP-14 (R-CHOP-14) would improve survival is undetermined. From January 2008, the principal investigator conducted a multi-center, prospective, controlled, randomized phase Ⅲ clinical trial (5010 project) to compare the efficacy and safety of first-line treatment with R-CHOP-21, R-CHOP-14 and CHOP-14 in adult patients with previously untreated DLBCL. In August 2010, analysis based on 163 subjects in Sun Yat-Sen University Cancer Center indicated that regimens containing rituximab, both R-CHOP-21 and R-CHOP-14, significantly improved short-term efficacy in contrast to CHOP-14 and R-CHOP-14 tended to improve survival compared with R-CHOP-21. Both the preliminary result of our study and the findings of recent international studies indicated that CHOP-14 was inferior to R-CHOP every 2 or 3 weeks, despite its superior efficacy to CHOP-21. So CHOP-14 was no longer considered as a standard treatment for DLBCL in the NCCN guideline since 2009 (economic reasons were preclusive). Consequently, we terminated the enrolment and randomization of CHOP-14 group from the view of ethics. However, whether R-CHOP-14 is more effective than R-CHOP-21 in adult patients with newly diagnosed DLBCL, high-risk patients would benefit from shortening treatment intervals and Chinese patients could tolerate dose-intense regimen R-CHOP-14 are uncertain. In order to administrate and control the quality of this study, the original 42 participating centers were reduced to 12 centers including four subsidiary hospitals of Sun Yat-Sen University and another 8 hospitals in GuangZhou.

On the basis of our previous studies, we prepare to investigate the efficacy and safety of R-CHOP-14 as the first-line treatment for CD20-positive untreated DLBCL with G-CSF prophylaxis in a multi-center, prospective, controlled, randomized phase Ⅲ clinical trial. The early-phase study of this trial has been registered on the website of http://clinicaltrials.gov/.

2. Objectives

2.1. Primary Objective

The primary objective of the study is to compare 5-year disease free survival (DFS) rate following treatment with R-CHOP chemotherapy every three weeks versus every two weeks in subjects with untreated CD20-positive diffuse large B-cell lymphoma.

2.2. Secondary Objectives

The secondary objective is to compare overall response rate (ORR), complete remission rate (CRR), overall survival (OS) and safety following treatment with R-CHOP chemotherapy every three weeks verus every two weeks in subjects with untreated CD20-positive diffuse large B-cell lymphoma.

3. Study Design

This is a prospective, multi-center, parallel, controlled, open-label, randomized (1:1) phase Ⅲ study of treatment with R-CHOP regimen every 3 weeks (R-CHOP-21 group) compared to treatment with R-CHOP regimen every 2 weeks (R-CHOP-14 group) in subjects with untreated CD20-positive diffuse large B-cell lymphoma.

Subjects with early-stage disease will receive a total of 3 to 6 cycles of R-CHOP chemotherapy. Subjects with advanced-stage disease will receive a total of 6 to 8 cycles of R-CHOP chemotherapy. After the completion of chemotherapy, additional radiation therapy will be added to subjects with early-stage or residual disease.

Screening:

The subjects or their legally acceptable representative will provide written informed consent. A history, physical examination, ECOG performance status, laboratory studies including blood routine, blood biochemistry, urinalysis and pregnancy test, electrocardiogram, CT imaging and bone marrow biopsy will be performed to determine baseline disease status and study eligibility, all of which must be performed ≤14 days prior to randomization.

Treatment:

Based upon their assignment, subjects will receive a standard R-CHOP regimen repeated every 2 or 3 weeks, which comprised rituximab (375 mg per square meter of body-surface area given intravenously on day 1), cyclophosphamide (750 mg per square meter given intravenously on day 2), doxorubicin (50 mg per square meter given intravenously on day 2), vincristine (1.4 mg per square meter given intravenously on day 2, up to a maximal dose of 2 mg), and prednisone (60 mg per square meter given orally per day for 5 days). Subjects with early-stage disease will receive a total of 3 to 6 cycles of R-CHOP chemotherapy. Subjects with advanced-stage disease will receive a total of 6 to 8 cycles of R-CHOP chemotherapy. After the completion of chemotherapy, additional radiation therapy will be added to subjects with early-stage or residual

disease. The dose of radiotherapy is 30-40 Gray.

4.Subject Selection Criteria

4.1. Subject Selection Criteria

4.1.1 Number Of Subjects

A total of 454 subjects will be randomized to R-CHOP-21 group or R-CHOP-14 group.

4.1.2 Inclusion Criteria

Subjects eligible for enrolment in this study must meet all of the following criteria:

1. Age ≥18 years
2. Histologically confirmed CD20(+) diffuse large B-cell lymphoma defined according to WHO classification
3. No previous treatments including radiotherapy, chemotherapy and surgery
4. Radiographically measurable disease, defined as:

   1) 2 or more clearly demarcated lesions/nodes with a long axis > 1.5 cm and short axis ≥ 1.0 cm

   OR

   2) 1 clearly demarcated lesion/node with a long axis > 2.0 cm and short axis ≥ 1.0 cm

5. ECOG performance status of 0, 1, 2, or 3
6. Life expectancy of at least 3 months in the opinion of the investigator
7. Normal bone marrow function (WBC≥3.5×10^9/L, HGB > 100 g/L, PLT > 90×10^{12}/L)
8. Normal liver and renal function
9. No history of other malignancies
10. No other serious diseases which conflict with the treatment in the present study
11. No concurrent treatments that conflict with the treatments in the present study (including steroids)
12. Patients should understand and are willing to participate in the study. Inform consent form is supposed to obtained before treatment
13. All patients should consent to adopt efficient contraception methods during the treatment

and 6 months after completion of the treatment. The pregnancy tests of women of childbearing potential should be negative before the treatment

4.1.3 Exclusion Criteria

Subjects meeting any of the following criteria are ineligible for this study:

1. Current or previous participation in the treatment phase of another interventional clinical study within 3 months prior to randomization
2. Lymphomas secondary to chemotherapy or radiotherapy for other malignancies
3. Secondary, transformed, relapsed, or refractory lymphoma
4. Primary central nervous system lymphoma or testicular lymphoma
5. History of allergic reaction to any ectogenic protein
6. Any previous treatments for lymphoma
7. History of other malignancies
8. Screening laboratory values:
    1) Neutrophils $<1.0\times10^9$/L
    2) Hemoglobin<80g/L
    3) Platelets $<90\times10^9$/L
9. Concurrent severe or active infectious disease requiring systemic antibiotics or antiviral, antifungal treatment
10. Uncompensated heart failure, dilated cardiomyopathy, coronary heart disease with ST segment depression on electrocardiography, or myocardial infarction in the past 6 months
11. Renal insufficiency not related to lymphoma (creatinine≥2×upper limit of normal)
12. Hepatic insufficiency not related to lymphoma (transaminase≥3×upper limit of normal, and/or total bilirubin≥2.0mg/dl)
13. Clinical symptoms of cerebral dysfunction; Severe psychiatric disease
14. Female patients who are lactating or pregnant
15. Known or suspected inability to fully comply with study protocol

4.2. Removal Criteria

Subjects who have participated in the study will be removed from statistical analysis for the following reasons:

1. Subjects who are ineligible for this study

2. Continuous treatment less than 2 cycles and objective response can not be assessed, but AE can be assessed

3. Deviation(s) from the protocol

4.3. Withdrawal Criteria

Subjects will be withdrawn from study treatment and visits for any of the following:

1. Inability to fully comply with study protocol

2. Initiation of alternative anti-lymphoma treatment, which will influence the assessment of response

3. Unacceptable toxicity

4. Best interest of the subject based upon the investigator's discretion

5. At the request of the study subject at any time and for any reason

The reason for withdrawal from study participation and the date must be documented in the CRF. The investigator must perform the last visit, including disease, response and AE assessment, all of which must be documented in the CRF.

5. Study Procedures

5.1. Treatment Assignment

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study. Upon completion of all the required screening assessments, eligible subjects will be centrally randomized using a randomization schedule generated by Sun Yat-sen University Cancer Center statistical department, which will assign subjects in a 1:1 ratio to R-CHOP-21 group or R-CHOP-14 group.

5.2. Study treatment

5.2.1. R-CHOP-21 Group (Rituximab In Combination With CHOP)

drugs	dose	route	time
Rituximab (R)	375mg/m^2	intravenous	Day 1
Cyclophosphamide (C)	750mg/m^2	intravenous	Day 2
Doxorubicin (H)	50mg/m^2	intravenous	Day 2

Vincristine (O)	2mg/m^2(up to a maximal dose of 2 mg)	intravenous	Day 2
Prednisone (P)	60mg/m^2	oral	Day2-6

Time for next dose: day 22

Total cycles: 3-6 cycles for early-stage disease and 6-8 cycles for advanced-stage disease

5.2.2. R-CHOP-14 Group (Rituximab In Combination With CHOP)

drugs	dose	route	time
Rituximab (R)	375mg/m^2	intravenous	Day 1
Cyclophosphamide (C)	750mg/m^2	intravenous	Day 2
Doxorubicin (H)	50mg/m^2	intravenous	Day 2
Vincristine (O)	2mg/m^2(up to a maximal dose of 2 mg)	intravenous	Day 2
Prednisone (P)	60mg/m^2	oral	Day2-6

Time for next dose: day 15

Total cycles: 3-6 cycles for early-stage disease and 6-8 cycles for advanced-stage disease

Granulocyte colony-stimulating factor will be given subcutaneously at a dose of 1.0 to 2.0 ug per kilogram of the body weight daily from day 7 for 6 to 8 days.

6. Criteria Of Continuous Treatment

Subjects meeting all of the following criteria will receive next dose on schedule:

1. Neutrophils and platelets recover after the low ebb of bone marrow suppression

2. Neutrophils **>** 1.5×10^9/L on day 1 of next cycle

3. Platelets **>** 100×10^{12}/L on day 1 of next cycle

If the critical values can not be reached, next dose must be delayed until recovery of neutrophils and platelets. Subjects whose treatment is delayed more than 21 days due to hematological toxicity will be withdrawn from the study treatment and the AE must be documented in the CRF.

7. Rules Of Dosage Adjustment To Cytotoxic Drugs

Dosage adjustment to cytotoxic drugs is not allowed only if next cycle be delayed more than 7 days due to neutropenia or thrombocytopenia.

If the treatment is delayed more than 7 days between two continuous cycles due to neutropenia or thrombocytopenia, hematology analysis will be repeated every 3 to 4 days until neutrophils and platelets recover to the critical values above, and the dosage of cytotoxic drugs in the next cycle will be adjusted.

Rules of dosage adjustment to cytotoxic drugs are as follows:

Next cycle is delayed no more than 7 days: no adjustment

Next cycle is delayed more than 8 days and no more than 14 days:

- Cyclophosphamide (C) 25% reduction
- Doxorubicin (H) 25% reduction
- Vincristine (O) No adjustment
- Prednisone (P) No adjustment

Next cycle is delayed more than 14 days and no more than 21 days:

- Cyclophosphamide (C) 50% reduction
- Doxorubicin (H) 50% reduction

- Vincristine (O) No adjustment
- Prednisone (P) No adjustment

Besides hematological toxicity, other organ toxicity should be taken consideration into dosage adjustment.

8. Efficacy Assessments

8.1. Criteria Of Efficacy Assessments

Complete remission (CR), partial remission (PR), stable disease (SD) or progressive disease (PD) will be assessed according to 1998 Revised Response Criteria for indolent and aggressive lymphoma by American and International Lymphoma Study Group as detailed in **attachment 1**.

8.2. Efficacy Endpoints

8.2.1. Primary Efficacy Endpoint

- Disease-free survival (DFS), defined as the interval between the time of complete remission and disease progression or death
- 5-year DFS rate, defined as the percent of subjects whose DFS reach 5 years

8.2.2. Secondary Efficacy Endpoints

- Overall response rate (ORR), defined as the percent of subjects who achieve complete remission (CR), complete remission unconfirmed (CRu) and partial remission (PR)
- Complete remission rate (CRR), defined as the percent of subjects who achieve complete remission (CR)
- Overall survival (OS), defined as the interval between randomization and death

8.3. Schedule of Efficacy Assessments

Disease assessments will be performed before randomization, after 2 cycles, 4 cycles, 6 cycles and 8 cycles of R-CHOP chemotherapy, during follow-up, respectively. All subjects who complete treatment or withdraw from the study must receive efficacy assessment. During follow-up period, efficacy assessment will be performed every three months for two years after completion of treatment, then every 6 months for three years, then every year.

8.4. Methods Of Efficacy Assessments

Visceral lesions must be assessed by contrast-enhanced CT or MRI scan. Superficial lesions must be assessed by physical examination and documented in original medical record. Suspected lesions could be screened by X-ray or ultrasound, which must be assessed by CT or MRI scan after confirmed.

9. Safety

9.1. Safety Endpoints

9.1.1. Vital Signs And Physical Examination

Before randomization and treatment of every cycle, vital fhsigns and results of physical examination must be documented.

The next 8 items must be performed before randomization and treatment of every cycle:

- Physical examination
- Heart rate
- Blood pressure
- Body temperature
- Rate of Respiration

- Body weight
- ECOG performance status (details in attachment 2)
- Signs of infection

9.1.2. Laboratory Studies

Before initiation of the study, the monitors will document the normal range of laboratory studies of every involved laboratory. During the study, the next items must be performed:

- Hematology: white cell counts and differential, hemoglobin, and platelet counts
- Total bilirubin (both direct bilirubin and indirect bilirubin must be documented when the total bilirubin elevates), alanine aminotransferase, aspartate aminotransferase, lactic dehydrogenase, alkaline phosphatase, albumin, total protein and urea nitrogen
- Serum creatinine and uric acid
- electrolytes (sodium, potassium, calcium, and magnesium)
- urinalysis (protein, glucose and erythrocyte)

9.1.3. Electrocardiogram

9.2. Toxicity Assessment Of Adverse Events (AE) and Serious Adverse Events (SAE)

The investigator is required to make an assessment of the toxicity grade of each AE or SAE reported. In this protocol, the toxicity grade of each AE/SAE will be evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0.

10. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE as outlined in Section 10.1 and Section 10.3.

10.1. Definition of an AE

Any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse.

All AEs and the toxicity grade of each AE/SAE according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 must be documented in the CRF. Clinical monitors must collect and verify detailed information of AEs when examining original medical records. All AEs should be followed up until resolved. AEs which will not be resolved during clinical observation such as loss of sight, neurotoxicity and deficiency of limbs are graded as unsolved AEs, the blank for resolved time of which don't need to be filled in the CRF.

10.2. Relationship of AEs

The investigator must assess the relationship between AEs and study treatment or concomitant drugs according to the following five categories:

1) Absolutely related: the occurrence of AEs is in accord with chronological sequence after medical procedure and known side effects of suspected drugs, which can resolve after suspension of the drugs and reoccur after reusing of the drugs.
2) Possibly related: the occurrence of AEs is in accord with chronological sequence after medical procedure and known side effects of suspected drugs, which can also occur due to the subject's disease status or other treatment methods.
3) Possibly unrelated: the occurrence of AEs is not in accord with chronological sequence after medical procedure or known side effects of suspected drugs, which can also occur due to the subject's disease status or other treatment methods.

4) Unrelated: the occurrence of AEs is not in accord with chronological sequence after medical procedure but in accord with known side effects of non-study treatment drugs. The AEs can also occur due to the subject's disease status or other treatment methods, disappear after improvement of the disease and suspension of other treatment and reoccur after repeating other treatment methods.

5) Unevaluated: there is no specific relationship between the occurrence of AEs and chronological sequence after medical procedure. The type of AEs is similar to known side effects of suspected drugs, which can also occur due to other drugs.

AEs which are in accord with the categories number 1, 2 and 5 above should be documented as AEs of this study.

The incidence of AEs=Number of subjects who develop AEs/total subjects×100%

10.3. Serious Adverse Events

10.3.1. Definition

A serious adverse event is any untoward medical occurrence that, at any dose:

1) Results in death

2) Is life-threatening

3) Requires hospitalization or prolongation of existing hospitalization

4) Results in disability/incapacity

5) Is a congenital anomaly/birth defect

Hospitalization or prolongation of existing hospitalization for social reasons, selective operation, examination or other treatment appointed prior to enrolment and events related to lymphoma progression will not be reported as an SAE.

10.3.2. Reporting of Serious Adverse Events

All SAEs will be reported promptly in the SAE reporting tables. Initial reports of all SAEs regardless of relationship to study treatment must be submitted to Sun Yat-Sen University Cancer Center Ethics Committee (phone number: 020-87343135) within 24 hours by the investigator and the follow-up information on previous reports must be submitted as soon as possible, including outcome of SAEs. If the SAE is death, the follow-up information on previous reports is not necessary.

11. Rules of Withdrawal

11.1. Subjects withdraw from the study

Subjects can withdraw from the study at any time for any reason without impact on the investigator's right to treat disease for subjects. Based upon the interest of subjects, the investigator has the right to request subjects to withdraw from the study for any reason including concomitant disease, adverse events or treatment failure. The core group of clinical study reserves the right to request subjects to withdraw from the study for deviation(s) from the protocol, administrative reasons, or other effective or ethical reasons.

The last assessment for subjects must be performed and documented in the CRF regardless of the time and reason for withdrawal. The reason for withdrawal from study participation must be documented in the CRF. All documents related to subjects should be completed. Despite withdrawal from the study, those subjects should be followed up and documented about their diseases until withdrawal of informed consents.

For subjects who withdraw from the study due to concomitant diseases or adverse events, the details must be documented in the CRF with other appropriate and valuable data attached.

11.2. Premature Termination of the Study

Reasons for premature termination of the study include external events, repetition of SAEs, growing incidence of treatment-related death and slow enrolment in the study. All subjects will

be informed of premature termination of the study by written consents. Any subjects who decide to discontinue participating in the study must report to the principal investigator.

12. Rules of Follow-Up

12.1. Follow-up Period

Starting after completion of treatment or withdrawal from the study for other reasons.

12.2. Visit Scheduling

Every three months for the first two years and then every six months until the study is completed.

12.3. Contents

The contents of every follow-up visit include complaints of subjects, physical examination, hematology, urinalysis, biochemistry and assessment of lymphoma. All of the results must be documented in the original medical record. Disease assessments should also be documented in the CRF.

13. Data Analysis And Statistical Considerations

13.1. Hypotheses

The primary endpoint is 5-year disease free survival rate. The null and alternative hypotheses are designed with the goal of demonstrating the superiority of R-CHOP-14 over R-CHOP-21.

Superiority will be determined using the following hypothesis:

H0: 5-year disease-free-survival rates for R-CHOP-14 and for R-CHOP-21 are the same.

H1: 5-year disease-free-survival rates for R-CHOP-14 and for R-CHOP-21 are not the same.

13.2. Study Design Considerations

This prospective, multi-center, parallel, controlled, open-label, randomized (1:1) phase Ⅲ study compares R-CHOP chemotherapy repeated every 3 weeks (R-CHOP-21 group) with R-CHOP chemotherapy repeated every 2 weeks (R-CHOP-14 group) in subjects with untreated CD20-positive diffuse large B-cell lymphoma. The primary outcome is 5-year disease free survival rate by intent-to-treat, and the study is designed to determine if R-CHOP-14 is superior to R-CHOP-21 in the study population. Base on the reported 5-year disease-free-survival rate of 50%

for R-CHOP-21, a clinically meaningful improvement in 5-year disease-free-survival rate would be 12% for R-CHOP-14.

13.2.1. Sample Size Assumptions

The sample size calculation is based on the primary endpoint, 5-year DFS rate, with the following assumptions:

- 5-year disease-free-survival rate for R-CHOP-21 group: 50%
- 5-year disease-free-survival rate for R-CHOP-14 group: 62%
- Hazard Ratio: 0.69
- a 1:1 randomization scheme
- a 5% two-sided risk of erroneously claiming a difference in the presence of no true underlying difference by log-rank test
- a 80% chance of successfully declaring a difference in the presence of a true underlying difference (power)
- duration of accrual: 36 months
- follow-up period: 60 months
- 5% percent of cases drop

Under the above assumptions, a total sample size of 454 subjects is required with approximately 228 events observed. Up to December, 2010, a total of 262 subjects have enrolled in the study with 138 subjects randomized to R-CHOP-21 group and 124 subjects randomized to R-CHOP-14 group in our early-phase study. Consequently, another 89 subjects and 103 subjects will be required for R-CHOP-21 group and R-CHOP-14 group, respectively.

13.2.2. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is 5-year disease free survival rate.

13.2.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include overall response rate, complete remission rate, overall survival and safety.

13.3. Data Analysis Considerations

13.3.1. Analysis Populations

The primary population will be the intent-to-treat (ITT) population, which is defined as all subjects randomized to one of the two treatment groups. This ITT population will be the primary population in reporting efficacy data.

A Per Protocol (PP) Population will exclude subjects with major protocol deviations that will impact the efficacy outcome. The Per Protocol Population will be used in the primary endpoint analysis to check the robustness of the result when using the ITT population. However, if the number of subjects in the PP population is not more than 5% smaller than the ITT population, the analysis will not be performed.

The safety population will include subjects who receive at least one dose of study treatment. This population will be used for all safety measurements. In the analysis, subjects will be grouped based on the treatment they receive regardless of how they are randomized.

13.3.2. Analysis Data Sets

The primary data set for efficacy will be based on the disease-free-survival (DFS) and overall response rate (ORR) assessments. The primary data set for safety will be the adverse events and the laboratory data sets.

The efficacy response will be assessed by the investigators and by the independent reviewers. Data will be summarized for investigators to assess response as well as for independent reviewer to assess response. Statistical inference for efficacy claims(s) will be based on the DFS and ORR data assessed by the independent reviewers.

13.3.3. Treatment Comparisons

13.3.3.1. Primary Comparisons of Interest

The primary treatment comparison of interest will be R-CHOP-21 vs. R-CHOP-14. This will be based on comparing the 5-year disease-free-survival rate when the total number of events reaches 228 (from both arms) using the ITT population.

The primary efficacy endpoint will serve as a gatekeeper for the interpretation of treatment comparisons for the ‘inferential’ secondary endpoints. If H0 is rejected at the 0.05 level, the conclusion will be that there is a treatment difference between R-CHOP-21 and R-CHOP-14, and the p-value for the ‘inferential’ secondary endpoints may be interpreted.

13.3.3.2. Other Comparisons of Interest

The secondary comparisons of interest will be R-CHOP-21 vs. R-CHOP-14, based on the overall response rate (ORR) and overall survival (OS). The ORR and OS will be considered as 'inferential secondary endpoints' and will be tested hierarchically only if the primary endpoint, 5-year DFS rate, is significant. Each hypothesis will be tested at alpha level 0.05. If the 5-year DFS rate is significant then the ORR will be tested and if significant, then the OS will be tested.

13.3.4. Analysis Plan

13.3.4.1. Baseline Data

Baseline characteristics will be summarized and described in a frequency list.

13.3.4.2. Efficacy Analyses

All the efficacy analyses will be based on the data assessed by the independent reviewer(s). Data assessed by the investigator will also be summarized/analyzed for supportive purpose.

13.3.4.2.1 Efficacy

- Complete remission rate: the percent of subjects who achieve complete remission and complete remission, unconfirmed in the intent-to treat (ITT) population
- Partial remission rate: the percent of subjects who achieve partial remission in the intent-to treat (ITT) population
- Disease progression rate: the percent of subjects whose disease progresse in the intent-to treat (ITT) population

13.3.4.2.2. Analysis of Efficacy

Disease-free-survival (DFS) is defined as the interval between the time of complete remission and disease progression or death. Overall survival (OS) is defined as the interval between randomization and death. Both DFS and OS will be tested based on a two-sided test, with a significance level of 0.05. Survival distributions will be estimated using the Kaplan-Meier method, and survival curves will be compared using log-rank test.

The number and proportion of subjects who achieve complete remission, partial remission and progressive disease will be provided. Pearson chi-square test or Fisher's exact test will be used to compare the proportion of subjects with complete remission, partial

remission and progressive disease for R-CHOP-21 vs. R-CHOP-14.

13.3.4.3. Analysis of Safety

Values of laboratory tests, vital signs and results of physical examination pretreatment, during treatment and post-treatment must be documented in original medical record and the CRF. The definition of adverse events has been detailed in previous section. Data of clinical symptoms, signs and laboratory tests will be summarized according to NCI CTCAE grade (version 3.0).

Categorical data such as adverse events and serious adverse events will be summarized by frequency and proportion of total subjects, which will be compared using Pearson chi-square test or Fisher's exact test between R-CHOP-21 group and R-CHOP-14 group. Quantitative data such as laboratory tests will be described using arithmetic average or median for central tendency and standard deviation or interquartile range for distribution range, which will be compared using t test or non-parametric test between the two groups.

14. Materials For the Study

All materials provided to study sites and investigators are as follows:

- The study protocol
- Informed consent
- CRF
- Manual for investigators
- Archives of the principal study site

The investigators should sign and date on the receipt when receiving materials above.

15. Ethical Considerations

15.1. Responsibility Of Investigators

The investigators have the responsibility for guarantee of the clinical study's compliance with the protocol, Chinese good clinical practice (GCP) guidelines and applicable laws and regulations.

15.2. Informed Consent Process

Prior to participation in the study, subjects must be informed about objectives, methods, possible benefits, potential risks and possible discomforts of the study by investigators. They also should be informed that participation in the study would be voluntary, they can withdraw from the study

at any time, there is no impact on the treatment of the disease whether they take part in the study and their privacy will be protected.

Subjects or their legally acceptable representative should have enough time to read the inform consent and raise queries. Written informed consent must be obtained from each subject, or their legally acceptable representative, prior to participation in the study and a copy of the informed consent would be reserved by subjects.

15.3. Good Clinical Practice (GCP)

This study will be conducted in accordance with the Declaration of Helsinki and Chinese Good Clinical Practice (GCP). The study will be conducted only if be approved by the ethical review committee of the principal study site. The investigators will guarantee that the study will be conducted in accordance with applicable laws and regulations, scientific and ethical principles of the People's Republic of China. If the protocol needs revision during the study, the revised version must be reapproved by the ethical review committee of the principal study site. If new data related to study treatment are discovered, the informed consent must be revised and the revision must be reapproved by the ethical review committee of the principal study site and subjects.

15.4 Protection of Subjects' Personal Data

Data collected in the study are limited to the efficacy and safety related to study treatment. Data will be collected and used in accordance with applicable laws and regulations.

16. Administrative Requirements

16.1. Revision Of The Protocol

Neither the investigator nor the applicant can revise the protocol without agreement of the opposite side. All revisions of the protocol must be released by the applicant institution.

16.2. Completion Of The Case Report Form (CRF)

The investigator will confirm that subjects are enrolled in the study according to the contents of the screening schedule. Examination and treatment must be performed in accordance with the protocol and relevant results must be documented in original medical record and the observation table of CRF. The table for concomitant drugs must be filled at the end of every cycle. After completion of the study, the medical staff who fill the CRF and superior doctors must review

whether the CRF is consistent with original medical record. Data which deviate from reference range markedly or lie out clinically acceptable range must be verified and illustrated by medical staff who fill the CRF and superior doctors.

16.3 Quality Control Of Data

The following measures will be adopted to insure the integrity, accuracy and reliability of the data:

- Choose qualified and experienced study sites and investigators
- Explain the protocol to investigators in detail by lectures or written materials and discuss solutions to possible issues together
- Verify the integrity, authenticity, accuracy and reliability of data by monitors at regular intervals

16.4. Study Monitoring

16.4.1 Objective

- Make sure the study is conducted in accordance with the currently approved protocol, ICH GCP, and all applicable laws and regulations
- Insure the integrity, reliability and coherence of data and coordinate the schedule between study sites

16.4.2. Contents

- Monitor and report the conduct of the study
- Verify the eligibility and original data of all subjects
- The CRFs are filled timely, accurately, completely and reliably
- Study drugs are administered to subjects in accordance with the protocol
- All AEs are recorded in the CRF
- All mistakes are corrected and signed by investigators timely
- Deliver various forms, materials and information including reference range of laboratory tests to keep the testing system in each study site consistent with the principal study site
- Whether the SAEs or death, which occur during the study, are related or unrelated to the study, the responsible investigator and institution must adopt relevant measures

16.5. Study Completion

After the follow-up of the last subject is finished, the investigator will promptly inform the applicant institution of the study.

16.6. Study Termination And Site Closure

The applicant institution reserves the right to terminate the study or close any study site at any time for reasons including (but not limited to) the following:

- Deviation(s) from the protocol
- Inability to recruit enough subjects
- Safety issues
- Evident inferior efficacy

16.7. Audit

Representatives of applicant institution may conduct quality assurance audits of the site and inspect all records related to the study. Drug administration agencies may conduct an audit at any time during or after completion of the study. In the event of an audit, the study site will be informed.

17. Progression Of The Study

A total of 454 subjects will complete the study in 8 years.

Initiation date of the study: January 2011

Completion date of the study: December 2018

18. Appendices

18.1. Appendix 1

Standardized response criteria for non-Hodgkin's Lymphomas

Bruce D. Cheson, Sandra J. Horning, Bertr Coiffier, Margaret A. Shipp, Richard I. Fisher, Joseph M. Connors, T. Andrew Lister, Julie Vose, Antonio Grillo-López, Anton Hagenbeek, Fernando Cabanillas, Donald Klippensten, Wolfgang Hiddemann, Ronald Castellino, Nancy L. Harris, James O. Armitage, William Carter, Richard Hoppe, George P. Canellos. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas, Journal of Clinical Oncology, Vol 17, Issue 4 (April), 1999: 1244

Response Criteria:

Complete remission requires the following:

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (eg, lactate dehydrogenase [LDH]) definitely assignable to NHL.

2. All lymph nodes and nodal masses must have regressed to normal size (≤1.5 cm in their greatest transverse diameter for nodes. 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. The determination of splenic volume or splenic index by CT scan are cumbersome and not widely used. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (≥20 mm biopsy core). Flow cytometric, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time. These studies should only be incorporated into trials examining important research questions.

CR/unconfirmed (CRu) includes those patients who fulfill criteria 1 and 3 above, but with one or more of the following features:

1. A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

Partial remission requires the following:

1. ≥50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase in the size of the other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by at least 50% in the SPD.
4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
5. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, eg, large-cell lymphoma or low-grade lymphoma (ie, small, lymphocytic small cleaved, or mixed small and large cells).
6. No new sites of disease.

Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).

Relapsed disease (CR, CRu) requires the following:

1. Appearance of any new lesion or increase by≥50% in the size of previously involved sites.
2. ≥50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

Progressive disease (PR, nonresponders) requires the following:

1. ≥50% increase from nadir in the SPD of any previously identified abnormal node for PRs or nonresponders.
2. Appearance of any new lesion during or at the end of therapy.

Response Criteria for Non-Hodgkin's Lymphoma

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	> 75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
Relapse/Progression	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance

18.2. Appendix 2

ECOG performance status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.