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Study Protocol

(Version No.: 1.0 Version Date: 2025.12.17)

Project Title: A Prospective, Multicenter, Phase II Clinical Study of Pomalidomide in Combination with an Anti-CD20 Monoclonal Antibody and Prednisone as First-Line Therapy for Indolent B-Cell Lymphoma

Sponsor: The First Affiliated Hospital of Soochow University

Responsible Department: Department of Hematology

Principal Investigator: Haiwen Huang

Investigator Statement and Protocol Signature Page

As the principal investigator of this research project, I will comply with the ethical principles of the Measures for Ethical Review of Biomedical Research Involving Humans issued by the Ministry of Health (2016), the WMA Declaration of Helsinki (2013), the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), and GCP. Under the guidance of the Good Clinical Practice for Drug Trials, I will conduct the study using the protocol approved by the Ethics Committee and in accordance with the requirements of this protocol, so as to ensure the scientific validity of the study and protect the health and rights of the participants.

Name: _____

Signature: _____

Date: _____

Protocol Synopsis

Study Objective	To explore the efficacy and safety of pomalidomide in combination with an anti-CD20 monoclonal antibody and prednisone as first-line therapy for indolent B-cell lymphoma
Sample Size	30 cases
Study Population	Patients with indolent B-cell lymphoma
Inclusion Criteria	1. Age ≥ 18 years, regardless of sex; 2. Confirmed diagnosis of follicular lymphoma (FL); 3. Histopathologically confirmed CD20-positive marginal zone lymphoma (MZL), including extranodal marginal zone lymphoma (MALT), splenic marginal zone lymphoma (SMZL), and nodal marginal zone lymphoma (NMZL); 4. Confirmed diagnosis of indolent mantle cell lymphoma (MCL); 5. Patients with a confirmed diagnosis of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL); 6. Confirmed diagnosis of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia; 7. Presence of indications for treatment of indolent B-cell lymphoma; 8. No prior systemic antitumor therapy for lymphoma; 9. ECOG-PS score 0-2; 10. Essentially normal bone marrow hematopoietic function, with routine blood tests as follows: white blood cell count >3000/uL, absolute neutrophil count ≥1.5 × 10^9/L (use of granulocyte colony-stimulating factor is allowed), platelet count ≥75 × 10^9/L (transfusion to reach this minimum platelet count is allowed), and hemoglobin ≥9.0 g/dL (prior red blood cell transfusion or use of recombinant human erythropoietin is allowed). If peripheral blood abnormalities are caused by lymphoma involvement of the bone marrow or spleen, neutrophils≥1.0 × 10^9/L and platelets≥50 × 10^9/L are acceptable (the investigator may determine at his/her discretion whether enrollment is appropriate); 11. Normal function of major organs: a. Hepatic function: serum bilirubin ≤2.0 × ULN; serum ALT and AST ≤2.5 × ULN; b. Renal function: creatinine clearance >30 mL/min; 12. Expected survival≥3 months as judged by the investigator; Voluntary written informed consent signed before trial screening;
Exclusion Criteria	1. Current or prior other malignancy, unless curative treatment has been performed and there has been no evidence of recurrence or metastasis within the past 5 years;

	2. Lymphoma involvement of the central nervous system or transformation to a higher-grade lymphoma; 3. Hepatic or renal dysfunction unrelated to lymphoma: alanine aminotransferase (ALT) >3 times the upper limit of normal, aspartate aminotransferase (AST) >3 times the upper limit of normal, total bilirubin (TBIL) >2 times the upper limit of normal, or serum creatinine >1.5 times the upper limit of normal; 4. Other serious medical conditions that would affect this study (e.g., uncontrolled diabetes, gastric ulcer, or other serious cardiopulmonary diseases). The investigator has the authority to make this determination; 5. Severe or uncontrolled infection; 6. Clinically manifest central nervous system dysfunction; 7. Major surgery within the past 30 days (excluding lymph node biopsy); 8. Pregnant or lactating women, or women of childbearing potential who have not used contraceptive measures; 9. Allergy to the study drug; Patients considered unsuitable for enrollment by the investigator.
Intervention Regimen	Induction therapy: One cycle every 28 days for 6 cycles; R (anti-CD20 monoclonal antibody): 375 mg/m^2/w in C1; 375 mg/m^2 on d1 in C2-6; P (pomalidomide): 4 mg/day on d2-22, C1-C6; P (prednisone): 100 mg/day on d1-5, C1-C6; Maintenance therapy: pomalidomide (4 mg/day, d1-14) and anti-CD20 monoclonal antibody (375 mg/m^2 on d1, once every 8 weeks) for 2 years
Primary Study Endpoint	Overall response rate (ORR) after treatment
Secondary Study Endpoints	Complete response rate (CR), progression-free survival (PFS), overall survival (OS), and adverse events (hematologic and non-hematologic toxicities)
Study Progress Plan	Expected trial start: January 2026 Expected completion of enrollment: December 2026 Expected trial end: December 2027
Statistical Analysis Methods	Sample size determination: This study plans to enroll 30 subjects. Statistical analysis: Overall, continuous variables (such as age) will be described using number of observations, mean, median, standard deviation, minimum, and maximum; categorical variables will be described using frequency and percentage for each category; Time-to-event variables will be summarized using the Kaplan-Meier

	method. If the data allow, medians and quartiles will be calculated. The numbers of events and censored observations will also be presented. Efficacy evaluation: The complete response rate, partial response rate, and objective response rate after study treatment will be summarized, and the objective response rate will be statistically tested with the 90% confidence interval reported. The Kaplan-Meier method will be used to estimate the median duration of response and its 90% confidence interval. The Kaplan-Meier method will also be used to estimate the medians and 90% confidence intervals for progression-free survival and overall survival.
Publication Form of Study Results	One SCI article

I. Study Background

Indolent B-cell non-Hodgkin lymphoma (B-iNHL) comprises a group of lymphomas with low malignancy, slow progression, and generally favorable prognosis, accounting for approximately one-third of all NHL cases and occurring predominantly in middle-aged and elderly populations[1]. Based on histopathology, immunophenotype, and cytogenetic/molecular genetic characteristics, B-iNHL can be classified into follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), lymphoplasmacytic lymphoma (LPL), and some unclassifiable indolent B-cell lymphomas or chronic B-cell lymphoproliferative disorders (B-LPDu). Common clinical features of B-iNHL include a high incidence in middle-aged and elderly individuals, an indolent clinical course, a risk of transformation into aggressive lymphoma, and responsiveness to therapy but difficulty in achieving cure[2].

Treatments for B-iNHL include rituximab (R) monotherapy, single-agent cytotoxic therapy, combination chemotherapy, immunochemotherapy, hematopoietic stem cell transplantation, immunomodulatory agents, and novel targeted therapies. For patients with indications for systemic therapy, rituximab-based immunochemotherapy is commonly used, including R-CHOP (rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone), R-CVP (rituximab + cyclophosphamide + vincristine + prednisone), and BR (bendamustine plus rituximab)[3–5]regimen. In recent years, with increasing attention to chemotherapy-related toxicities, chemotherapy-free regimens have attracted growing interest.

The RELEVANCE study[6,7] compared the R^2 regimen (lenalidomide plus rituximab) with rituximab plus chemotherapy (R-CHOP, R-B, or R-CVP) in 1,030 patients with previously untreated FL. The results showed no statistically significant difference between the two groups in the complete response (CR)/CRu rate at 120 weeks (48% vs 53%) after a median follow-up of 37.9 months; the 3-year progression-free survival (PFS) rates were 77% and 78%, respectively. Another multicenter phase II trial[8] further confirmed the substantial efficacy of the R^2 regimen in previously untreated FL, with an overall response rate (ORR) of 95% and a CR rate of 72%; the 5-year PFS and overall survival (OS) rates were 70% and 100%, respectively. These findings support the R^2 regimen as a reasonable treatment option for previously untreated FL. In addition,

the R^2 regimen has also shown favorable efficacy in other B-iNHL subtypes. One study enrolled 27 patients with previously untreated MZL and reported an ORR of 89% and a median PFS of 53.8 months[9]. Another study[10] of the R^2 regimen in mucosa-associated lymphoid tissue (MALT) lymphoma showed an ORR of 80%, a median time to best response of 3.6 months, and a CR rate of 54%. Therefore, owing to efficacy comparable to immunochemotherapy and the absence of chemotherapy-related toxicity, the R^2 regimen has become one of the standard regimens recommended by domestic and international guidelines, particularly for elderly patients.

However, lenalidomide, as a second-generation immunomodulatory agent, is still associated with adverse reactions such as rash, renal toxicity, thrombosis risk, hematologic toxicity, and risk of secondary malignancies, which partially limits its clinical use. Pomalidomide is a third-generation IMiD developed based on structural optimization of lenalidomide, with T-cell costimulatory activity 10 times that of lenalidomide. Because pomalidomide and lenalidomide bind to different CRBN sites, no cross-resistance exists between the two[11]; patients resistant to lenalidomide may still achieve renewed remission with pomalidomide-based combination therapy[12]. Multiple preclinical studies have shown that pomalidomide can stimulate dendritic cells and increase tumor necrosis factor and interferon-gamma, thereby altering the cytokine microenvironment, increasing the number of NK cells, and enhancing the activity of rituximab[13,14]. In terms of safety, due to its unique molecular structure, pomalidomide is less frequently excreted unchanged through the kidneys, has less impact on renal function, and is associated with a lower incidence of rash[15,16].

Recent studies have further explored the potential of pomalidomide-based combinations in B-iNHL. A study reported at ASH 2025 showed that pomalidomide combined with obinutuzumab and a BTK inhibitor in TP53-mutated mantle cell lymphoma (MCL) achieved a CR rate of 86.7% and an ORR of 100% after 6 cycles, and all evaluable patients achieved minimal residual disease (MRD) negativity[17]. Another phase I study evaluated a novel BTK inhibitor in combination with everolimus and pomalidomide for relapsed/refractory CLL and B-cell lymphoma; the results showed that the regimen was safe and effective, and it is currently advancing to phase II[18]. Although systematic studies of pomalidomide in indolent B-cell lymphoma are still lacking in China, we hypothesize that rituximab plus pomalidomide (the RP regimen) may have efficacy comparable to or even better than that of the R2 regimen, with improved safety.

Based on the above background, this study is designed to use the PRP regimen (pomalidomide + anti-CD20 monoclonal antibody + prednisone) as induction therapy, followed by maintenance therapy with pomalidomide plus an anti-CD20 monoclonal antibody. Through a multicenter, prospective, single-arm exploratory clinical study, this study aims to evaluate the efficacy and safety of this regimen in patients with initial treatment indolent B-cell lymphoma.

II. Objectives and Endpoints of the Clinical Study

1. Primary Objective

To explore the efficacy and safety of pomalidomide in combination with an anti-CD20 monoclonal antibody and prednisone as first-line therapy for indolent B-cell lymphoma.

2. Secondary Objectives

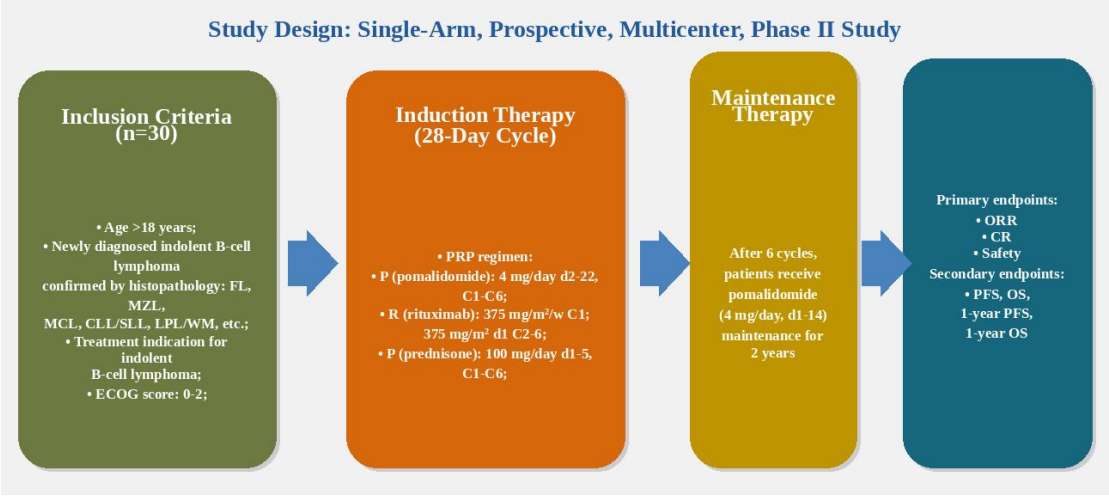
Overall response rate (ORR), complete response rate (CR), progression-free survival (PFS), overall survival (OS), and adverse events (hematologic and non-hematologic toxicities) after treatment.

III. Study Design

3.1 Overview

This is a prospective, multicenter, phase II clinical study.

This study uses a single-arm design and will exploratorily enroll 30 patients. A total of 30 evaluable patients are planned to be screened and enrolled across participating centers.



This project is expected to start in January 2026 and end in December 2027.

Note: Any change in the actual duration of the project will not constitute a protocol deviation.

3.2 Study Stopping Rules

This study may be discontinued for any reason, including medical or ethical reasons affecting continued conduct of the study or difficulty in patient recruitment, at the discretion of the initiating party.

3.3 End of Study

The study will end when all patients have completed treatment under this protocol and the subsequent 24-month visit/follow-up period, or when the last patient dies, is lost to follow-up, or withdraws informed consent, whichever occurs first.

IV. Study Protocol and Study Drug

4.1 Study Drug Composition

Brief Introduction to Pomalidomide Capsules

Generic name: Pomalidomide Capsules

English name: Pomalidomide Capsules

Chinese pinyin: Bomadu'an Jiaonang

Main ingredient: Pomalidomide

Chemical name: (RS)-4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione.

Molecular formula: C13H11N3O4

Molecular weight: 273.24

Excipients: mannitol, pregelatinized starch, sodium stearyl fumarate, and empty gelatin capsules.

Description: The contents of this product are yellow powder or granules.

Pomalidomide Capsules: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Strengths: 4 mg/capsule and 1 mg/capsule;

Storage conditions: Store sealed below 30°C.

The 1 mg/capsule strength of study drug will be provided for dose reduction.

4.2 Treatment Regimen

Induction therapy: R (anti-CD20 monoclonal antibody): 375 mg/m^2/w in C1; 375 mg/m^2 on d1 in C2-6; P (pomalidomide): 4 mg/day on d2-22, C1-C6; P (prednisone): 100 mg/day on d1-5, C1-C6; one cycle is 28 days, for a total of 6 cycles.

Maintenance therapy: Maintenance therapy with pomalidomide (4 mg/day, d1-14) and an anti-CD20 monoclonal antibody (375 mg/m^2 on d1, once every 8 weeks) for 2 years.

4.3 Dose Modification and Treatment Delay

4.3.1 Dose Modification for Hematologic Adverse Reactions

When patients start pomalidomide treatment, the absolute neutrophil count should be at least 500/μL and the platelet count should be at least 50,000/μL. If hematologic adverse reactions occur during pomalidomide treatment, the dose should be adjusted according to Table 1.

Table 1 Instructions for Dose Modification Due to Hematologic Adverse Reactions

Toxicity	Dose Modification Plan
Neutropenia ANC <500/μL or febrile neutropenia (fever ≥38.5°C and ANC <1,000/μL)	Interrupt treatment with this product and monitor complete blood counts weekly. After ANC recovers to≥ 500/μL, treatment may be resumed at 3 mg once daily.
Subsequent decrease to <500/μL	Interrupt treatment with this product until ANC recovers to≥500/μL. When treatment is resumed, reduce the previous daily dose by 1 mg each time*.
Thrombocytopenia Platelets <25,000/μL	Interrupt treatment with this product and monitor complete blood counts weekly. After the platelet count recovers to >50,000/μL, treatment may be resumed at 3 mg once daily.
Subsequent decrease to <25,000/μL	Interrupt treatment with this product until the platelet count recovers to >50,000/μL. When treatment is resumed, reduce the previous daily dose by 1 mg each time*.

* If the patient still cannot tolerate treatment after dose reduction to 1 mg once daily, pomalidomide should be permanently discontinued.

ANC = absolute neutrophil count

4.3.2 Dose Modification for Non-Hematologic Adverse Reactions

Pomalidomide should be permanently discontinued in the event of angioedema, severe allergic reaction, grade 4 rash, skin exfoliation, blistering, or any other severe skin reaction.

In the event of other grade 3 or grade 4 adverse reactions, treatment with this product should be interrupted. After the adverse reaction has recovered to grade 2 or below, treatment may be resumed under physician guidance, and the daily dose should be reduced by 1 mg from the dose before interruption.

4.3.3 Concomitant Use with Strong CYP1A2 Inhibitors

During pomalidomide treatment, concomitant use of strong CYP1A2 inhibitors should be avoided whenever possible, and alternative therapies should be considered. If concomitant use with a strong CYP1A2 inhibitor cannot be avoided, the starting dose of pomalidomide should be reduced from 4 mg to 2 mg.

4.4 Prophylactic Medication

In the original clinical trials of pomalidomide capsules, venous thromboembolic events (VTEs) were reported as serious adverse reactions in patients receiving pomalidomide, and all patients were required to receive prophylactic or antithrombotic therapy. In this clinical trial, investigators should carefully decide on prophylactic measures after assessing each patient's underlying risk factors.

For reference, among subjects receiving pomalidomide in this trial, it is strongly recommended that subjects at risk for thromboembolic events receive daily prophylactic aspirin or another prophylactic agent during pomalidomide treatment. In subjects at high risk for VTE, low-molecular-weight (LMW) heparin, heparin (at the recommended dose for DVT/PE prophylaxis according to the package insert), or warfarin (maintaining an INR of 2.0) is strongly recommended.

Use of these prophylactic medications should be considered for subjects enrolled in this clinical trial. The choice of VTE prophylaxis depends on investigator judgment and should take

into account the risk of thrombosis, bleeding risk, and patient compliance with VTE prophylaxis, with individualized treatment adapted to the subject's individual risk/benefit profile. (Choice based on the judgment of the treating physician.)

4.5 Drug Interactions and Precautions for Concomitant Medications

CYP3A, CYP1A2, or P-gp inhibitors: Concomitant administration of pomalidomide with strong inhibitors of CYP1A2 or CYP3A (e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir, etc.) or P-gp may increase exposure and should be avoided.

CYP3A, CYP1A2, or P-gp inducers: Concomitant administration of pomalidomide with strong inducers of CYP1A2 or CYP3A (e.g., rifampin, carbamazepine, phenytoin, etc.) or P-gp may decrease exposure and should be avoided.

Cigarette smoking may reduce exposure to pomalidomide due to CYP1A2 induction. Investigators should warn patients that smoking may reduce the efficacy of pomalidomide, and patients who smoke must stop smoking during the trial.

V. Efficacy Evaluation

5.1 Efficacy Evaluation

Efficacy will be evaluated according to the 2014 revised Lugano criteria for malignant lymphoma response assessment (see Appendix II).

5.2 Efficacy Endpoints Observed in the Study

(1) Primary efficacy endpoints:

Overall response rate (ORR) and complete response rate (CR) after treatment

(2) Secondary efficacy endpoints

Secondary efficacy endpoints: progression-free survival (PFS), overall survival (OS), and adverse events (hematologic and non-hematologic toxicities).

5.3 Definitions of Endpoints

(1) Progression-free survival (PFS): Defined as the time interval from enrollment to disease progression or death, whichever occurs first, in the intent-to-treat (ITT) population. For patients who withdraw from the trial without progression or without a recorded date of disease progression, the date of the last examination will be used as the endpoint date.

(2) Overall response rate (ORR): Defined as the percentage of subjects in the per-protocol population and the intent-to-treat population who achieve CR + PR after treatment.

(3) Complete response rate (CRR): Defined as the percentage of subjects in the per-protocol population and the intent-to-treat population who achieve CR after treatment.

(4) Overall survival (OS): Defined as the time interval from enrollment to death in the intent-to-treat (ITT) population. If a patient remains alive or survival status is unknown, the date of death will be censored at the most recent time point at which the patient was known to be alive.

(5) Duration of response (DR): Defined as the time interval from the first recorded disease response to the first recorded evidence of PD in the intent-to-treat (ITT) population. For patients who withdraw from the trial without progression or without a recorded date of disease progression, the date of the last examination will be used as the endpoint date.

(6) Toxicity and adverse effects: Toxicity will be evaluated according to NCI CTCAE 5.0 (Appendix III).

VI. Subject Admission Criteria and Exclusion Criteria

6.1 Inclusion Criteria

1. Age ≥ 18 years, regardless of sex;

2. Confirmed diagnosis of follicular lymphoma (FL);

3. Histopathologically confirmed CD20-positive marginal zone lymphoma (MZL), including extranodal marginal zone lymphoma (MALT), splenic marginal zone lymphoma (SMZL), and nodal marginal zone lymphoma (NMZL);

4. Confirmed diagnosis of indolent mantle cell lymphoma (MCL);

5. Patients with a confirmed diagnosis of chronic lymphocytic leukemia (CLL)/small lymphocytic

lymphoma (SLL);

6. Confirmed diagnosis of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia;

7. Presence of indications for treatment of indolent B-cell lymphoma;

8. No prior systemic antitumor therapy for lymphoma;

9. ECOG-PS score 0-2;

10. Essentially normal bone marrow hematopoietic function, with routine blood tests as follows: white blood cell count >3000/uL, absolute neutrophil count ≥1.5 × 10^9/L (use of granulocyte colony-stimulating factor is allowed), platelet count ≥ 75 × 10^9/L (transfusion to reach this minimum platelet count is allowed), and hemoglobin ≥9.0 g/dL (prior red blood cell transfusion or use of recombinant human erythropoietin is allowed). If peripheral blood abnormalities are caused by lymphoma involvement of the bone marrow or spleen, neutrophils≥1.0 × 10^9/L and platelets ≥ 50 × 10^9/L are acceptable (the investigator may determine at his/her discretion whether enrollment is appropriate);

11. Normal function of major organs:

a. Hepatic function: serum bilirubin ≤2.0 × ULN; serum ALT and AST ≤2.5 × ULN;

b. Renal function: creatinine clearance >30 mL/min;

12. Expected survival≥3 months as judged by the investigator;

13. Voluntary written informed consent signed before trial screening;

6.2 Exclusion Criteria

1. Current or prior other malignancy, unless curative treatment has been performed and there has been no evidence of recurrence or metastasis within the past 5 years;

2. Lymphoma involvement of the central nervous system or transformation to a higher-grade lymphoma;

3. Hepatic or renal dysfunction unrelated to lymphoma: alanine aminotransferase (ALT) >3 times the upper limit of normal, aspartate aminotransferase (AST) >3 times the upper limit of normal, total bilirubin (TBIL) >2 times the upper limit of normal, or serum creatinine >1.5 times the upper limit of normal;

4. Other serious medical conditions that would affect this study (e.g., uncontrolled diabetes,

gastric ulcer, or other serious cardiopulmonary diseases). The investigator has the authority to make this determination;

5. Severe or uncontrolled infection;

6. Clinically manifest central nervous system dysfunction;

7. Major surgery within the past 30 days (excluding lymph node biopsy);

8. Pregnant or lactating women, or women of childbearing potential who have not used contraceptive measures;

9. Allergy to any of the drugs used;

10. Patients considered unsuitable for enrollment by the investigator.

6.3 Criteria for Early Withdrawal

1. Subjects have the right to withdraw from the study at any time;

2. The subject or the subject's legally authorized representative requests withdrawal from the study;

3. The subject is lost to follow-up;

4. Disease progression (PD).

6.4 Criteria for Subject Interruption/Discontinuation of Study Drug

1. The subject requests discontinuation of study drug treatment;

2. Drug interruption for more than 30 days;

3. Occurrence of disease progression;

4. Pregnancy occurs in a subject during the study;

5. If adverse events occur, the investigator shall discontinue the medication following discussion;

6. Overall deterioration of health status, making continued participation in the trial impossible;

7. A significant protocol deviation such as the subject being found ineligible after enrollment;

8. Loss to follow-up;

9. The sponsor terminates the study;

10. Death of the subject;

11. Other reasons for which the investigator believes trial treatment cannot be continued.

VII. Study Procedures and Examinations

7.1 Screening Visit

The screening visit is recommended to be performed within 2 weeks before treatment in Cycle 1. The recommended examinations are as follows:

Medical history, prior treatment history, vital signs, physical examination, and collection of demographic data: sex, age, date of birth, ECOG performance status (Appendix I), and symptoms;

Laboratory tests: routine blood tests (white blood cell count, ANC), hepatic and renal function (total bilirubin, conjugated bilirubin, ALT, AST, alkaline phosphatase, total protein, albumin, blood urea nitrogen, creatinine, gamma-glutamyl transferase, lactate dehydrogenase), electrolytes (potassium, sodium, chloride, calcium, phosphorus), beta-2 microglobulin, LDH, hepatitis B serology, HBV-DNA, syphilis, HIV, HCV, complete coagulation profile (PT, APTT, TT, Fg), routine urine and stool tests, thyroid function, myocardial enzyme profile, and glycated hemoglobin;

Cardiac function tests: echocardiography; electrocardiogram;

Bone marrow aspiration and biopsy;

Imaging examinations: whole-body PET/CT; enhanced CT for positive sites (enhanced MRI for Waldeyer's ring, breast lesions, central nervous system involvement, etc.);

Pregnancy test.

7.2 Treatment-Period Visits

Before the start of each cycle: routine blood tests (routine blood tests at least once weekly during dosing), hepatic and renal function, electrolytes, β-2 microglobulin, LDH, complete coagulation profile, routine urine and stool tests, hepatitis B serology or HBV-DNA, thyroid function, myocardial enzyme profile, and glycated hemoglobin;

Once every cycle: vital signs, ECOG score, physical examination (including skin toxicity, nausea, fatigue, etc.), and quality-of-life score assessment;

Before the start of each cycle: cardiac function tests, including echocardiography and

electrocardiogram;

AE observation and recording at any time;

After initiation of dosing, imaging examination of lesion sites and efficacy evaluation will be performed once after completion of Cycle 2 during induction therapy (enhanced CT and ultrasound every 2 cycles; PET-CT every 6 cycles);

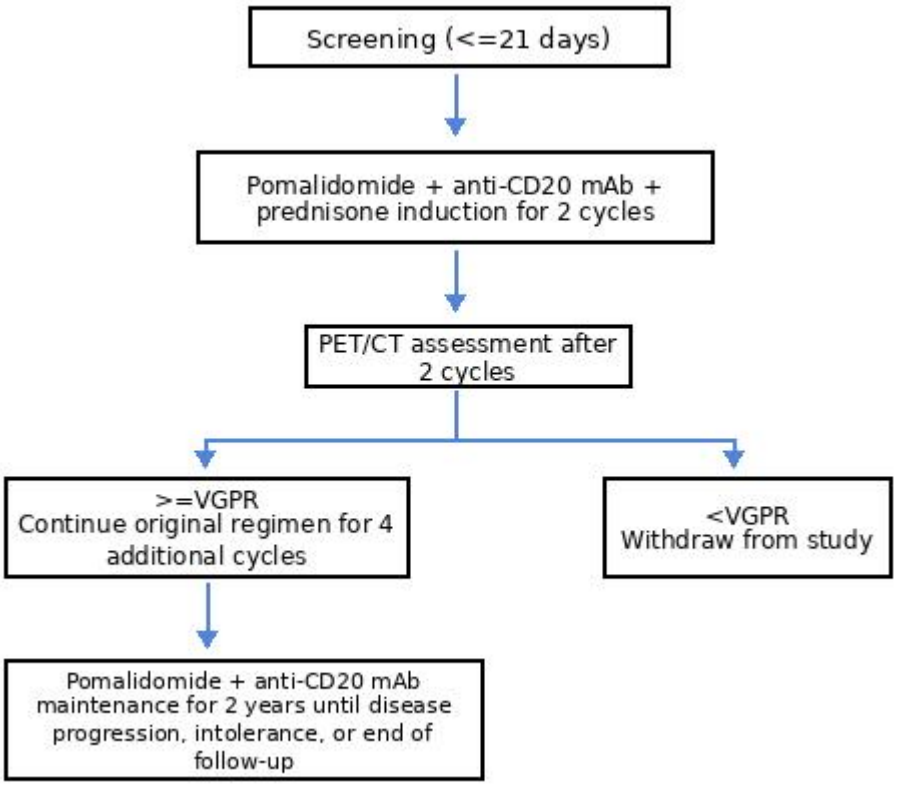
During maintenance therapy, imaging examination of lesion sites and efficacy evaluation will be performed once every 6 cycles (enhanced CT and ultrasound every 6 cycles; PET-CT every 12 cycles);

7.3 Data Collection During Post-Treatment Follow-Up

Patients who discontinue study drug for any reason will enter the subsequent follow-up phase. Follow-up observations will not require additional hospital visits. Investigators will contact patients by telephone once every 2-3 months. The following parameters should be recorded during follow-up: time of disease progression or death; other antitumor treatments; SAEs occurring during the study; and survival (telephone follow-up may be used, and records must be retained).

7.4 Study Flow

This study consists of a screening period (Day -28 to Day 0), treatment period, end-of-treatment period, and follow-up period.



VIII. Subject Dropout/Loss to Follow-Up and Withdrawal

8.1 Subject Dropout and Management

All subjects who meet the inclusion criteria, sign the informed consent form, and have entered the clinical trial but do not complete the observation period specified in the protocol will be considered dropout cases. These include:

1) Subjects with poor compliance during the trial, affecting efficacy and safety evaluations.
2) Cases in which the treatment course is not completed and the subject withdraws from the trial, is lost to follow-up, or dies for various reasons unrelated to disease or treatment.
3) Cases with incomplete data that affect efficacy and safety judgments.

After a subject drops out, the investigator should make every effort to contact the subject

through home visits, scheduled follow-up visits, telephone calls, letters, or other means, inquire about the reason, record the last dosing time, complete all feasible evaluation and examination items, and make detailed records.

8.2 Loss to Follow-Up and Management

If a subject cannot return for a visit or be reached by telephone, at least three telephone contact attempts should be made to obtain the necessary subject information. All attempts should be documented in the source documents. The subject should be considered "lost to follow-up" for the current study visit or telephone contact, and contact attempts must be repeated at the next follow-up time point. A subject may be deemed lost to follow-up and the end-of-study form completed only after the subject cannot be contacted at the final follow-up.

8.3 Subject Withdrawal

Each subject should remain in contact with study personnel during the clinical trial until the specified follow-up period is completed. However, participation in any clinical trial is voluntary, and subjects have the right to withdraw from the trial at any time without any penalty or loss of benefits. Patients who withdraw from this project may, depending on their condition, be advised to receive a conventional chemotherapy regimen subsequently.

Possible reasons for subject withdrawal include, but are not limited to, the following:

1) Subjects have the right to withdraw from the study at any time;
2) The subject or the subject's legally authorized representative requests withdrawal from the study;
3) The subject is lost to follow-up;
4) Disease progression (PD). The reason for the patient's withdrawal from the trial must be recorded truthfully.

8.4 Subject Exclusion

1) Incorrect dose or method of administration (actual drug exposure dose less than 80% or greater than 120%);

2) Poor patient compliance, failure to use the study drug on time and at the prescribed dose; or unauthorized mid-study drug switching or addition of drugs prohibited by this protocol, which the investigator confirms has a serious impact on efficacy assessment;
3) Use of antitumor treatments other than those specified in this protocol during the trial, such as chemotherapy, surgery, or investigational drug therapy;
4) Erroneous enrollment of a subject who does not meet the criteria;
5) Patients who did not receive study medication.

Note: Patients meeting criteria 1-3 will be included in the safety analysis.

IX. Adverse Events

9.1 Adverse Events (AEs)

An AE refers to any unfavorable medical occurrence in a subject or clinical trial participant and does not necessarily have a causal relationship with treatment. Therefore, an AE may be any unfavorable or unintended sign (e.g., including abnormal laboratory findings), symptom, or transient drug-related disease, and whether it is related to medication should be considered.

For management purposes, adverse events occurring before and after treatment are both considered adverse events. Therefore, safety monitoring (reporting of adverse events or serious adverse events) should be conducted from subject enrollment through the end of the study. Adverse events occurring between signing of the informed consent form and initiation of study treatment are also considered AEs.

9.2 Serious Adverse Events (SAEs)

An SAE refers to any unfavorable medical occurrence occurring at any drug dose that results in death or is life-threatening. Note: "Serious" and "life-threatening" are defined as an event in which the subject is at risk of death when the adverse event occurs; this does not refer to an adverse event that hypothetically might have led to death if it had been more severe. If an SAE occurs during the trial, the investigator should immediately take appropriate protective measures for the subject and report it to the principal investigator within 24 hours. The investigator should

complete the Serious Adverse Event Report Form and sign and date the report.

SAEs include:

A. Death or life-threatening event

B. Hospitalization or prolonged hospital stay

C. Permanent disability

D. Carcinogenicity

E. Teratogenicity

1) Other events that should be handled as SAEs:

Drug exposure during pregnancy/lactation. In principle, pregnancy and lactation are exclusion criteria. If pregnancy occurs during the study, the patient should immediately withdraw from the study and inform the investigator immediately, and the patient should be followed throughout pregnancy and after delivery. Even if both mother and infant are completely normal without any adverse event, the outcome should be recorded. Even if pregnancy itself is not an SAE, it should be reported using the SAE report form.

Disease progression is generally not considered an SAE (however, if the signs and symptoms of disease progression meet SAE criteria, it may be reported as an SAE).

Death itself is an outcome and is not considered an SAE (the primary cause of death, i.e., the primary AE leading to death, should be recorded and reported as the SAE, and "death" should be reported as the outcome of the corresponding AE; if there is no definite cause of death to report, death itself may be reported as an SAE).

Death occurring within 1 month after a subject starts medication should be reported as an SAE; after a subject has been on medication for more than 1 month, if death occurs due to disease progression, it will not be reported as an SAE.

2) Events that should not be handled as SAEs:

Because of the severity of the disease in this study, certain conditions identified as SAEs may need to be excluded from immediate reporting:

A. Optional hospitalization and surgical treatment

B. Optional hospitalization for the purpose of simplifying treatment or research procedures

9.3 Assessment of Adverse Events

1) Severity of adverse events

The investigator will evaluate and record all adverse events according to the following criteria.

AEs should be described using medical terminology. All AEs should be recorded in the relevant section of the case report form (CRF), and the SAE report form (including initial or follow-up reports) should also be completed as applicable. All cases participating in the trial must be included in the summary. Reasons must be provided for cases that withdraw midway or are excluded at summary. If a death or severe toxicity occurs during the trial, a detailed individual case report should be prepared. For fatal cases, the cause of death should be determined, with particular attention to the relationship with the investigational drug. Unresolved adverse events should be followed up, and all adverse events should be tracked until properly resolved or stabilized.

The following aspects of each event should be recorded in the CRF:

- Time of occurrence (start time) and time of recovery (end time)
- AEs will be graded by the investigator according to the definitions of NCI CTCAE v5.0:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Activities of daily living (ADL)

* Instrumental activities of daily living refer to preparing meals, shopping for clothes, using the telephone, managing money, etc.

** Self-care activities of daily living refer to bathing, dressing and undressing, eating,

toileting, taking medications, etc., and do not imply being bedridden.

- The possible relationship between the AE and the investigational medication will be assessed using a five-category classification: definitely related, probably related, possibly related, probably unrelated, and unrelated. The first three categories are judged to be related to the investigational drug. When calculating the incidence of adverse reactions, the sum of the first three categories will be used as the numerator, and all subjects included in the safety analysis will be used as the denominator.
- Measures taken with respect to the drug (none, treatment discontinued, dose reduced, treatment delayed, intravenous infusion rate slowed) and other measures (none, concomitant medication, hospitalization required or hospitalization prolonged, surgery performed, treatment delayed, treatment discontinued).
- Outcome will be defined as follows: recovered without sequelae, recovered with sequelae, not recovered but no treatment required, not recovered and treatment required, or death. Whether a change in toxicity grade/severity is serious: yes or no. If a patient experiences the same AE several times, each occurrence must be recorded and reassessed.

  Criteria for determining whether an abnormal objective examination result should be reported as an adverse event are as follows:

- The examination result is associated with concomitant symptoms (and/or);
- The examination result requires additional diagnostic examination or therapeutic measures/surgical intervention (and/or);
- The examination result leads to a change in study drug dose or discontinuation of the trial, requires additional concomitant medication, or other treatment (and/or);
- The investigator believes that the examination result should be reported as an adverse event.

Repeating an abnormal test, by itself, does not constitute an adverse event if none of the above criteria is met. Any abnormal examination result determined to be erroneous does not need to be reported as an adverse event.

9.4 Management and Follow-Up of Adverse Reactions

9.4.1 Management of Adverse Reactions

(1) Thrombocytopenia: Routine blood tests are required at each follow-up visit. If grade 1 thrombocytopenia occurs, routine blood tests will be performed once weekly; if grade 2 thrombocytopenia occurs, routine blood tests will be required twice weekly; if grade 3 thrombocytopenia occurs, routine blood tests will be performed every other day. In the event of grade 3 thrombocytopenia, study medication should be stopped and platelet-raising therapy administered until recovery to grade 1 thrombocytopenia, after which treatment may be resumed. Platelet-raising agents are permitted during treatment.

(2) Leukopenia: Routine blood tests are required at each follow-up visit. If grade 2 leukopenia occurs, routine blood tests will be performed once weekly; if grade 3 leukopenia occurs, routine blood tests will be required twice weekly. In the event of grade 3 leukopenia, study medication should be stopped and G-CSF administered to increase white blood cells until recovery to grade 1 leukopenia, after which treatment may be resumed. G-CSF treatment to increase white blood cells is permitted during treatment.

(4) Febrile neutropenia: For grade 1 fever, oral antibiotics should be given; for grade 2 or higher, treatment should be suspended until body temperature has been normal for 3 days, after which treatment may be resumed.

(5) Gastrointestinal symptoms, such as nausea, vomiting, and constipation: Symptomatic supportive care should be strengthened. In general, treatment discontinuation or dose reduction is not required. Drugs such as 5-HT3 receptor antagonists may be routinely given to prevent gastrointestinal symptoms such as nausea and vomiting, and laxatives may be used to prevent constipation.

(6) Dizziness, fatigue, and somnolence: Thalidomide should be administered orally at bedtime; patients should be encouraged to engage in appropriate activity and prevent falls.

9.4.2 Follow-Up of Adverse Events

The investigator should follow up on all adverse events (including serious adverse events).

Follow-up may be performed periodically according to the condition until a final outcome is reached, and the follow-up process and outcome of the adverse event should be recorded.

X. Data Management

10.1 Case Report Form

The investigator should record relevant data for each patient in the study medical record in a timely and truthful manner. The investigator or authorized personnel should enter relevant data into the case report form within the specified time. All relevant data from each follow-up visit for each subject during the trial should be recorded in a timely and truthful manner, with confirmation and signature. To protect patient privacy, patient names will be coded. After completion of the study, copies of the electronic case report forms will be retained by the sponsor and the study site, respectively.

10.2 Database Establishment

The data manager designated by the statistical expert will prepare the electronic case report form files and system in advance. For questionable data, the system will promptly prompt the investigator or authorized personnel to verify and modify the data. After the database has been reviewed and confirmed to be accurate, the data will be locked by the principal investigator, data manager, statistician, and monitor. To ensure data security, unrelated personnel will be unable to enter or modify data. Electronic case report data must be backed up. Any data change may be made only after a jointly signed consent is obtained from the principal investigator, statistician, and data manager.

10.3 Data Lock

The automatic validation system will check data deviations in the eCRF and generate corresponding query forms, allowing study site personnel to modify and verify entered data. The system will automatically retain an audit trail of all data modifications. The data will then be transmitted to the data statistics unit through a secure virtual private network. When the principal

investigator, sponsor, statistical analyst, and data management personnel are present together, the analysis datasets will be determined and the reviewed data will be locked. In principle, locked data files will not be changed.

10.4 Selection of Data Sets for Statistical Analysis

- Full Analysis Set (FAS): In accordance with the intent-to-treat (ITT) principle, efficacy analysis will include all enrolled cases who receive at least one dose of study drug.
- Per-Protocol Set (PPS): Cases that comply with protocol-specified treatment, have good compliance, complete the required contents of the case report form, and do not use prohibited medications during the trial.
- Safety Analysis Set (SAS): All enrolled patients who receive at least one dose of study drug and have post-dose safety records.

XI. Responsibilities of Collaborator and Investigator

11.1 Collaborator

- Provide investigators with support such as study materials, and explain the protocol and completion of various documents to investigators before clinical study initiation;
- Assign clinical monitors to conduct regular monitoring visits;
- Ensure that monitors can maintain contact with investigators at any time by telephone, fax, and email;
- The monitor will supervise investigators in conducting the clinical study in accordance with the approved protocol, verify that study drugs are dispensed and returned according to relevant regulations, and ensure consistency between trial records and source data in the clinical trial.

11.2 Investigator

- Has received training in GCP and this study protocol and has sufficient time to conduct the trial according to the protocol;

- Before patient enrollment, provides patients with detailed information related to this study, obtains patient consent, and ensures that the informed consent form is signed;
- The investigator is obligated to take necessary measures to ensure patient safety. When an adverse reaction occurs, the investigator should immediately handle it according to relevant requirements and report it to the principal investigator. Serious adverse reactions should be followed up;
- Complete the case report form carefully and in a timely manner;
- Actively cooperate with regular visits by the clinical monitor;
- Retain complete laboratory test records, clinical records, and patients' original medical records;
- To ensure evaluation and supervision of the clinical trial by the National Medical Products Administration and the sponsor, the study site should uniformly retain all study materials, including confirmation of all patients (to allow effective verification of different records), all original signed informed consent forms, and detailed original drug dispensing records, for a retention period of 5 years. All materials of this clinical trial are owned by the collaborator. Except for the national drug regulatory authority, investigators may not provide them to any third party in any form without the sponsor's written consent.

XII. Ethical Standards and Informed Consent

This clinical trial must be conducted in accordance with the Declaration of Helsinki (2008 version) and relevant Chinese standards and regulations for clinical trial research. Before initiation of the clinical trial, the trial protocol will be developed, agreed upon and signed by the investigator and sponsor, and submitted to the hospital Ethics Committee for approval before implementation. If this protocol needs to be revised during actual conduct of the clinical trial, the revised protocol must again be submitted to the Ethics Committee for approval before implementation. If important new information related to the study drug is identified, the informed consent form must be amended in writing, submitted to the Ethics Committee for approval, and patient consent must be obtained again.

Before initiation of the clinical trial, the investigator must provide patients with detailed

information about the clinical trial, including the nature and purpose of the trial, possible benefits and risks, and the rights and obligations of patients. The clinical trial may begin only after the patient fully understands the information, agrees to participate, and signs the informed consent form.

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Appendix I: ECOG Performance Status Criteria

Score	Performance Status Criteria
0	Fully active; no difference in activity compared with before disease onset.
1	Able to walk freely and perform light physical activity, including ordinary housework or office work, but unable to perform strenuous physical activity.
2	Ambulatory and capable of self-care, but unable to work; up and about more than half of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely bedridden; unable to care for self.
5	Death.

Appendix II: 2014 Lugano Response Assessment Criteria

Response	Site	PET-CT (Metabolic Response)	CT (Radiographic Response)[d]
Complete Response	Lymph nodes and extranodal sites	Score 1, 2, or 3a on the 5-point scale (5-PS)b,c, with or without a residual mass	All of the following: Target lymph nodes/nodal masses must regress to a longest transverse diameter (LDi) ⩽1.5 cm; No extranodal disease sites
	Nonmeasured lesions	Not applicable	Absent
	Organ enlargement	Not applicable	Returned to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in bone marrow	Normal morphology; if indeterminate, immunohistochemistry negative
Partial Response	Lymph nodes and extranodal sites	Score 4 or 5b with reduced uptake compared with baseline and reduced residual mass. Interim result indicates disease response End-of-treatment result indicates residual disease	All of the following: ⩾50% decrease in SPD of up to 6 measurable target lymph nodes and extranodal lesions; If a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value; if no longer visible, assign 0 x 0 mm For nodules >5 mm x 5 mm but smaller than normal size, use the actual measurements for calculation
	Nonmeasured lesions	Not applicable	Absent/normal, regressed, but not increased
	Organ enlargement	Not applicable	The portion of spleen length exceeding normal must regress by >50%
	New lesions	None	None

	Bone marrow	Residual uptake higher than normal marrow uptake but reduced compared with baseline (diffuse uptake different from chemotherapy effects is allowed). If persistent focal changes are present in bone marrow despite nodal response, consider further evaluation by biopsy or MRI, or interval scanning.	Not applicable
No Response or Stable Disease	Target lymph nodes/nodal masses and extranodal lesions	Score 4 or 5b, with no significant change in FDG uptake compared with baseline at interim or end of treatment, and no new or progressive lesions	<50% decrease from baseline in SPD of up to 6 largest measurable lymph nodes and extranodal sites; all criteria for progressive disease not met
	Nonmeasured lesions	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change compared with baseline	Not applicable
Progressive Disease	Individual target lymph node/nodal mass or extranodal lesion	Score 4 or 5b with increased intensity of uptake compared with baseline and/or new FDG-avid foci consistent with interim or end-of-treatment assessment	At least one of the following PPD progression criteria is required: A single lymph node/lesion must be abnormal and have the following features: LDi >1.5 cm and an increase of $\geqslant$ 50% from the PPD nadir, and an increase from nadir in LDi or SDi of 0.5 cm (for lesions $\leqslant$ 2 cm) or 1.0 cm (for lesions >2 cm) In the setting of splenomegaly, spleen length must increase by >50% of the prior increase from baseline; if no prior splenomegaly, there must be an increase of at least 2 cm above baseline New or recurrent splenomegaly
	Nonmeasured lesions	None	New or definite progression of existing nonmeasurable lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than	Regrowth of previously resolved lesions

	another etiology (e.g., infection or inflammation). If the etiology of new lesions is uncertain, biopsy or interval scanning may be considered.e	Any new lymph node >1.5 cm in any diameter; Any new extranodal site >1.0 cm in any diameter; if any diameter is <1.0 cm, it must be clearly present and attributable to lymphoma Any assessable lesion of any size that is clearly attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New lesion or recurrent lesion

Notes:

a In many patients, a score of 3 indicates a favorable prognosis with standard treatment, especially on interim scans. However, in PET-based de-escalation trials, it is preferable to consider a score of 3 as an inadequate response (to avoid undertreatment);

b See the PET five-point scale (5-PS);

c It is generally recognized that uptake may be greater than normal mediastinum and/or liver in extranodal sites with high physiologic uptake, such as Waldeyer's ring, or with activation in the spleen/bone marrow (e.g., due to chemotherapy or myeloid colony-stimulating factors). In this setting, complete metabolic response (CMR) may be inferred if uptake at initially involved sites is not greater than surrounding normal tissue, even if the tissue has high physiologic uptake;

d Response in FDG-avid lymphomas should be assessed by PET-CT; diseases that can usually be followed by CT alone include CLL/SLL and marginal zone lymphoma;

e False-positive PET scan results associated with infectious or inflammatory conditions may be observed. Biopsy of the affected site remains the gold standard for confirming new or persistent disease.

PET five-point scale (5-PS):

1 no uptake above background; 2 uptake $\leqslant$ mediastinum; 3 uptake > mediastinum but $\leqslant$ liver; 4 uptake moderately > liver; 5 uptake markedly higher than liver and/or new lesions; X new area of uptake unlikely to be related to lymphoma

SPD: sum of the products of the perpendicular diameters of multiple lesions

LDi: longest transverse diameter of a lesion

SDi: shortest axis perpendicular to LDi

PPD: cross product of LDi and the perpendicular diameter

Measurable dominant lesions: Select up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions that are clearly measurable in two diameters. Nodes should preferably come from different regions of the body and, where possible, should include mediastinal and retroperitoneal regions. Non-nodal lesions include lesions in solid organs (e.g., liver, spleen, kidney, lung, etc.), gastrointestinal involvement, and palpable skin lesions.

Nonmeasured lesions: Any lesions that are not selected as measurable dominant disease but are assessable should be considered nonmeasured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant measurable disease, or sites that do not meet measurability requirements but are still considered abnormal. They also include all suspected disease sites that are difficult to quantify by measurement but are assessable, including pleural effusion, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

Appendix III: Criteria for Evaluation of Antitumor Drug Toxicity and Adverse Reactions (NCI-CTCAE 5.0)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin <LLN-10.0 g/dL; <LLN-6.2 mmol/L; <LLN-100 g/L	Hemoglobin <10.0-8.0 g/dL; <6.2-4.9 mmol/L; <100-80 g/L	Hemoglobin <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Febrile neutropenia	—	—	ANC <1000/mm^3 with a single temperature >38.3°C (101°F) or sustained temperature ⩾ 38°C (100.4°F) for more than 1 hour.	Life-threatening consequences; urgent intervention indicated	Death
Neutrophil count decreased	<LLN-1500/mm^3; <LLN-1.5 x 10^9/L	<1500-1000/mm^3; <1.5-1.0 x 10^9/L	<1000-500/mm^3; <1.0-0.5 x 10^9/L	<500/mm^3; <0.5 x 10^9/L	—
Platelet count decreased	<LLN-75,000/mm^3; <LLN-75.0 x 10^9/L	<75,000-50,000/mm^3; <75.0-50.0 x 10^9/L	<50,000-25,000/mm^3; <50.0-25.0 x 10^9/L	<25,000/mm^3; <25.0 x 10^9/L	—

White blood cell count decreased	<LLN-3000/mm^3; <LLN-3.0 x 10^9/L	<3000-2000/mm^3; <3.0-2.0 x 10^9/L	<2000-1000/mm^3; <2.0-1.0 x 10^9/L	<1000/mm^3; <1.0 x 10^9/L	—
Nausea	Loss of appetite without alteration in eating habits	Decreased oral intake without significant weight loss, dehydration, or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition, or hospitalization indicated	—	—
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, total parenteral nutrition, or hospitalization indicated	Life-threatening consequences	Death
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest; limiting self-care ADL	—	—
Fever	38.0-39.0°C (100.4-102.2°F)	>39.0-40.0°C (102.3-104.0°F)	>40.0°C (>104.0°F) ⩽ 24 hours	>40.0°C (>104.0°F) for >24 hours	Death
Generalized edema	Findings on physical examination; 1+ pitting edema	Limiting instrumental ADL; oral medication indicated	Limiting self-care ADL; IV medication indicated; skin breakdown	Life-threatening consequences	—

Malaise	Discomfort or feeling of ill health	Discomfort or feeling of ill health; limiting instrumental ADL	Discomfort or feeling of ill health; limiting self-care ADL	—	—
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	—	—
Lung infection	—	Moderate symptoms; oral therapy indicated (antibiotic, antifungal, or antiviral medication)	IV antibiotic, antifungal, or antiviral therapy indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output; limiting instrumental ADL	Increase of ⩾7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care	Life-threatening consequences; urgent intervention indicated	—

			ADL		
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema indicated	Persistent symptoms with regular use of laxatives or enemas indicated; limiting instrumental ADL	Obstipation requiring manual evacuation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Somnolence	Mild increase in sleep requirement	Moderate increase in sleep requirement	Severe increase in sleep requirement	—	—
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Upper respiratory infection	—	Moderate; oral therapy indicated (antibiotic, antifungal, or antiviral	IV antibiotic, antifungal, or antiviral therapy indicated; invasive intervention	Life-threatening consequences; urgent intervention indicated	Death

		therapy)	indicated		
Insomnia	Mild difficulty falling asleep, staying asleep, or early awakening	Moderate difficulty falling asleep, staying asleep, or early awakening	Severe difficulty falling asleep, staying asleep, or early awakening	—	—
Arterial thromboembolism	—	—	Urgent intervention indicated	Life-threatening consequences: hemodynamic or neurologic instability; organ damage; distal extremity loss.	Death
Thromboembolic event	Medical intervention not indicated (e.g., superficial thrombosis)	Medical intervention indicated	Urgent medical intervention indicated (e.g., pulmonary embolism or intracardiac embolus)	Life-threatening consequences with hemodynamic or neurologic instability	Death
Tumor lysis syndrome	—	—	Present	Life-threatening consequences; urgent intervention indicated	Death

Peripheral sensory neuropathy	Asymptomatic	Moderate; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	—
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death