# Protocol

## Camrelizumab plus GVD Chemotherapy in Relapsed/Refractory Primary Mediastinal B-cell Lymphoma: a single-arm, open-label, phase 2 trial

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# Title Page

**Camrelizumab plus GVD Chemotherapy in Rituximab-refractory Primary Mediastinal B-cell Lymphoma**

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**Funding Sponsor** the National Natural Science Foundation of China
National Key Research and Development Program of China
Fostering Funds of Chinese PLA General Hospital for National Excellent Young Scholar Science Fund

| | |
|---|---|
| **Study Product** | Camrelizumab (SHR-1210); Gemcitabine, Vinorelbine, Doxorubicin |
| **Original Protocol** | May 1, 2017 |

**CONFIDENTIAL**



**STUDY TEAM**

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## Summary

**Protocol title:** Camrelizumab plus GVD Chemotherapy in Relapsed/Refractory Primary Mediastinal B-cell Lymphoma (rrPMBCL)

**Investigational Product(s):** Combined regimen of GVD chemotherapy (Day 1) consisted with gembitabine (1000 mg/m$^2$), vinorelbine bitartrate (30 mg) and doxorubicin hydrochloride liposomal (20 mg/m$^2$) plus 200 mg SHR-1210 (Day 2) every 3 weeks, intravenously

## Study objectives:

**Primary objectives:**

To assess the objective response (complete and partial response) and safety of SHR-1210 plus GVD chemotherapy as salvage therapy for rrPMBCL.

**Secondary objectives**

To evaluate the complete response, time to response (TTR), duration of response (DOR) and progression-free survival (PFS) of SHR-1210 plus GVD chemotherapy in subjects with rrPMBCL.

**Exploratory objectives**

To detect the baseline expression levels of PD-L1 in lymphoma cells from biopsy samples, the phenotype and activity of peripheral blood T cells, serum cytokines and chemokines before and during the treatment, and analyze the association with clinical response.

## Treatment plan

Subjects will receive study drugs as Figure 1.

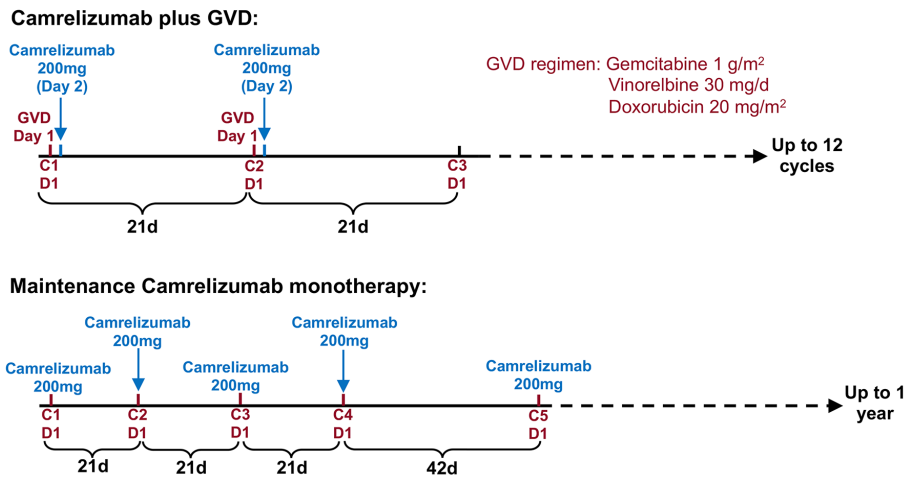


**Figure 1. Treatment plan**

## Study Population

Subjects must meet all eligibility criteria, including the following:

**Key inclusion criteria:**

1) Subjects with histologically proven relapsed or refractory PMBCL who recurrent or refractory to at least one rituximab-containing regimen.
2) 18 to 80 years of age.
3) Subjects must have at least one bulky mediastinal mass (the longest diameter ≥ 5 cm).
4) ECOG performance of 0 or 2.
5) Subjects must have received at least one line of previous rituximab-containing therapy, and must be off therapy for at least 4 weeks prior to Day 1
6) Subjects must have adequate bone marrow, live, renal, lung and heart functions.
7) Signed informed consent.

**Key exclusion criteria:**

1) Subjects with any autoimmune disease or history of syndrome that requires corticosteroids or immunosuppressive medications.
2) Serious uncontrolled medical disorders or active infections, pulmonary and intestinal infection especially.
3) Active alimentary tract hemorrhage or history of alimentary tract hemorrhage in 1

month.

4) CNS involvement.

5) Prior organ allograft or allogeneic bone marrow transplantation.

6) Autologous stem-cell transplantation (ASCT) within the previous 3 months.

7) Other antitumor antibodies within 4 weeks, previous treatment with anti-PD-L1, anti-PD-L2, anti-CTLA-4 or agents targeting T-cell co-stimulation.

8) Unsuitability for the trial, based on clinical judgment.

## Study assessment

**Safety evaluation:**

Adverse events will be assessed continuously during the study and for 3 months post last treatment. Adverse events will be evaluated according to the NCI CTCAE, Version 5.0. Subjects should be followed until all treatment-related adverse events have recovered to baseline or are deemed irreversible by the investigator.

**Efficacy evaluation:**

Objective response rate (ORR), complete remission rate, time to response, duration of response (DOR), and progression-free survival (PFS) will be evaluated using the Lugano Response Criteria for Non-Hodgkin's Lymphoma.

**Experimental biomarkers detection:**

Available blood samples and tumor tissues will be collected at baseline and specified time points for all subjects. The peripheral T cell phenotype, activity and serum cytokines/chemokines were detected by FACS, and tumor PD-L1 levels were assessed by immunohistochemical pathological analysis and multiplex immunostaining.

# 1. Introduction

## 1.1 Background

Primary mediastinal large B-cell lymphoma (PMLBCL) is an infrequent aggressive B cell lymphoma, which comprises approximately 2 - 4% of non-Hodgkin lymphomas (nHL) and 10% of diffuse large B-cell lymphoma (DLBCL)[1]. PMBCL was not recognized as a discrete entity until 1994 by the revised European-American classification of lymphoid neoplasms[2], and then regarded as a unique subtype of DLBCL since the 2008 World Health Organization classification of lymphoid neoplasms[3]. PMBCL typically presents with compressive symptoms from the large mediastinal mass, and typically affects adolescents and young women in their third or fourth decade[4]. But the gender preponderance is only seen in Caucasians, moreover, other ethnicities rather than display Caucasians play as a poor worse prognosis factor of PMBCL[5]. Although the optimal first-line therapy is more controversial in PMBCL than other subtypes of nHL, the introduction of rituximab into the chemotherapy (EPOCH, CHOP and ICE) have significantly increased the response and survival outcomes of PMBCL[6, 7]. However, unsatisfactory responses to frontline therapy involve 15–20% of patients, who would experience relapsed/refractory disease with a dismal prognosis[8-10].

The treatment of patients with relapsed/refractory PMBCL (rrPMBCL) requires the salvage therapies, the option of which is limited[7, 11, 12]. The common salvage regimen of rrPMBCL is salvage immunochemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT), as in DLBCL, and few patients (0 - 20%) could proceed to ASCT[4, 8, 13]. Salvage immunochemotherapy regimens include R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), R-ICE (rituximab, ifosfamide, carboplatin and etoposide) or the potentially less toxic R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin), and the response to the salvage chemotherapy regimen has been regarded as an important outcome predicator[10, 14, 15]. Since rrPMBCL is often resistant to chemotherapy, the response rate to salvage

regimens are unacceptable low. There is an urgent medical need for more effective treatment options in rrPMBCL. Because of the rarity of the disease and the consequent inability to design an adequately powered randomized study, the clinical trials focused on PMBCL was rare and all performed in no randomized[6]. The data of novel therapies in PMBCL often obtained from trials in related hematological malignancies as well as 'basket-trials' where patients are chosen by genetic mutation rather than malignancy type[4].

Despite classified as a rare type of DLBCL, PMBCL represents a molecular signature reminiscent of classical nodular sclerosis Hodgkin's lymphoma (nsHL), including a third of gene expressing profile, abnormalities on chromosome 9p (in nearly three quarters of cases) and the CD30 expression (although weaker)[16-18]. Amplification of the chromosome 9p24.1, detected in at least 50 - 70% of patients, accounts for the overexpression of Janus kinase 2 (JAK2) and the consequent activation of the JAK-signal transducer and activator of transcription (JAK/STAT) pathway[19-21]. Aberrant activation of JAK/STAT not only implicates in several aspects of disease, but also involved in tumor immune evasion, and these make it a rational therapeutic target[22]. The JAK2-specific inhibitor, ruxolitinib, has been evaluated in rrHL (n = 14) and PMBCL (n = 6) via a pilot phase 2 clinical trial. All 6 PMBCL patients progressed rapidly after the first 2 cycles[23].

Expression of CD30 is another shared characteristic between PMBCL and HL. Even with a weaker and more heterogeneous staining, CD30 is expressed in more than 80% of cases[18]. Based on this, brentuximab vedotin (BV), the chimeric CD30-specific IgG1 antibody conjugated to the microtubule-disrupting agent, has been approved for HL and assessed in $CD30^+$ PMBCL by a phase 2 trial. A total of 15 patients were enrolled, and the overall response rate (ORR) was 13.2%, and only 2 PR were observed. Furthermore, One of the 2 patients in PR after the 4th cycle early progressed just a few administrations later. Given the disappointing results, the study was terminated early[24].

Chimeric antigen receptor T cell (CAR-T) treatment is an exciting prospect in fighting hematological malignancy. Abxicatragene Ciloleucel (axi-cel, KTE-C19)

targets ubiquitous B cell marker CD19, and has been approved by Food and Drug Administration (FDA) and European Commission approval for patients with rrDLBCL and PMBCL based on the phase 1/2 clinical trial (ZUMA-1)[25]. Among 101 patients, including 8 PMBCL cases, the ORR was 82% with a CR of 58% at 1 year. Unfortunately, there is not yet any data regarding other specific CAR-T treatments specifically in PMBCL.

**1.2 Rational for SHR-1210**

As previously mentioned, amplification of chromosome 9p24.1 and constitutively activated JAK/STAT pathway are common in PMBCL patients. Activation JAK/STAT pathway is able to upregulate the expression of PD-L1/L2, the ligands of programmed death-1 (PD-1), by exerting a positive feedback[19]. Moreover, PD-L1/L2 also locate in chromosome 9p24.1, and the amplification of this region results in elevated expression of PD-L1/L2[16, 26, 27]. The interaction of PD-L1/L2 with PD-1 expressed on tumor-infiltrating T cells lead to T-cell anergy and exhaustion, which consequently caused tumor immune escape. Blockade of PD-1 can restore an adequate immunosurveillance against the neoplasm and enhance T-cell-mediated antitumor response[28-30].

The safety and efficacy of PD-1 blockade monotherapy in rrPMBCL have been confirmed by two serial trials (Keynote-013 and Keynote-170) with 41% objective response rate (ORR) and 13% complete response (CR) rate[31, 32]. The data had led to FDA approval for the use of pembrolizumab, PD-1 antibody, in rrPMBCL patients progressed after two or more lines of prior therapy.

SHR-1210, an original drug autonomously manufactured by Shanghai Hengrui Medicine Co., Ltd in China, is a humanized anti-PD-1 monoclonal antibody. The heavy chain of SHR-1210 is immunoglobulin G4 (IgG4), and the light chain is immunoglobulin kappa (IgK), which is expressed in the supernatant of Chinese hamster ovary stable cell line. SHR-1210 has proven to achieve similar response rates with other PD-1 blockades in relapsed/refractory HL and recurrent or metastatic

nasopharyngeal carcinoma[33, 34]. Moreover, a phase I trial of SHR-1210 in patients with nasopharyngeal carcinoma was carried out and a fixed dose of 200 mg/dose (equivalent to 3 mg/kg calculated dose) was selected by the authors for an expansion phase part of their study[35]. The dose of 200 mg of SHR-1210 was used in other trials for cancers of other organs, including NSCLC, HCC, esophagus cancer, and nasopharyngeal carcinoma, as described in the investigator's brochure. Thus, we chose SHR-1210 (camrelizumab) as 200 mg per dose every 3 weeks in this study.

### 1.3 Rational for GVD chemotherapy

Considering a median response time of 2.9 months, PD-1 blockade monotherapy is not approved for patients required urgent cytoreduction, which is a common desirability in patients with rrPMBCL, especially refractory PMBCL. Based on the urgent cytoreductive therapy requirement, chemotherapy will be a rational choice for rrPMBCL patients in need of salvage treatment. The common salvage chemotherapy for rrPMBCL include RICE, DHAP, ESHAP, GDP, mini-BEAM, and so on. These intensive regimens are associated with significant hematologic toxicity and a 2%–5% treatment-related death rate. The majority of patients with rrPMBCL have experienced heavily pretreated history and resistance to several chemotherapy regimens. Introduce of noncross-resistant drugs to promote the response rates with low toxic effects sound to be a very reasonable choice[1, 4].

The GVD chemotherapy regimen consisted with gemcitabine, vinorelbine and doxorubicin has been confirmed with limited toxicity and a favorable response in both relapsed/refractory aggressive nHL or HL. The ORR achieved 80% and 36% in HL and nHL, respectively[36, 37]. Besides, gemcitabine is not commonly used in rrPMBCL, and it will provide an opportunity to overcome the chemoresistance. Furthermore, gemcitabine has been reported to directly target the myeloid-derived suppressor cells (MDSCs) to reprogram the immunosuppressive tumor microenvironment which will improve the efficacy of PD-1 blockade therapy[38].

The chemotherapeutic drugs, gemcitabine, vinorelbine and doxorubicin, have

been marketed. We used the standard combination in this clinical trial: Gemcitabine, 1g/$m^2$/day; Vinorelbine Bitartrate, 30 mg/day; and Doxorubicin Hydrochloride Liposomal, 20 mg/$m^2$/day.

## 2. Study objectives

### 2.1 Research hypothesis

SHR-1210 plus GVD chemotherapy could serve as a salvage chemoimmunotherapy with promising efficacy and manageable safety profile for patients with relapsed/refractory PMBCL (rrPMBCL).

### 2.2 Objectives

#### 2.2.1 Primary objectives

To assess the objective response (complete and partial response) and safety of SHR-1210 plus GVD chemotherapy as salvage therapy for rrPMBCL.

#### 2.2.2 Secondary objectives

To evaluate the complete response, time to response (TTR), duration of response (DOR) and progression-free survival (PFS) of SHR-1210 plus GVD chemotherapy in subjects with rrPMBCL.

#### 2.2.3 Exploratory objectives

To detect the baseline expression levels of PD-L1 in lymphoma cells from biopsy samples, and analyze the association with clinical response.

To detect the phenotype and activity of peripheral blood T cells, serum cytokines and chemokines before and during the treatment of combination therapy, and assess the correlation with the outcomes.

# 3. Ethical considerations

## 3.1 Ethical conduct of the study

This single-center, open-label phase II trial was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and with Good Clinical Practice guidelines provided by the International Conference on Harmonization. The study was approved by the Institutional Review Board (IRB) of the Chinese PLA General Hospital (review broad identifier, S2016-127-01).

The IRB will also function as data and safety monitoring committee.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive IRB approval/favorable opinion prior to initiation of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

Principal investigator is responsible for providing IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. The research team will provide this information to the principal investigator so that he can meet these reporting requirements.

## 3.2 Subjects data protection

The Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation.

Precautions are taken to preserve confidentiality and prevent data being linked to the identity of the subjects. In exceptional circumstances, however, certain individual might see both the data and the personal identifiers of a subject. Regulatory authorities may require assess to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

### 3.3 Informed Consent

Written informed consent to participate was obtained from each patient before enrollment. Investigators must describe the protocol, alternative therapies, and the risks and benefits of each to the individual signing the consent. The investigational nature and research objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts and potential benefits, and alternative therapies will be clearly and fully informed to the patient. The attached informed consent contains all elements required for consent. In addition, the Principal Investigator or his designee will be available to answer all patient questions throughout their participation in the protocol.

Investigators must: 1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood. 2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study. 3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. 4) Obtain the IRB’s written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information. 5) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The Principal Investigator or his designee should fully inform the subject of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

### 3.4 Change to the protocol and informed consent form

If there are any substantial changes to the study protocol, then these changes will be documented in d study protocol amendment and where required in a new version of the study protocol.

The amendment in to be approved by IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

### 3.5 Audits and inspections

Ethics Committee performs audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice, guideline of the International Conference on Harmonization, and any applicable regulatory requirements.

## 4. Selection of subjects

### 4.1 Inclusion criteria

Patients must fulfill all of the following inclusion criteria to be eligible for admission to the study:

1) ≥ 18 years old.
2) Patients with histologically proven relapsed or refractory PMBCL who recurrent or refractory to at least one rituximab-containing regimen.

   Refractory was defined as a lack of response to, or progression during first-line rituximab-containing treatment.

   Relapsed was defined as recurrence within 6 months after first-line rituximab-containing treatment.

3) Patients must have at least one bulky mediastinal mass (the longest diameter ≥ 5 cm).

4) Eastern Cooperative Oncology Group (ECOG) performance 0 − 2.

5) Subjects must have received at least one line of previous rituximab-containing therapy, and must be off therapy for at least 4 weeks prior to Day 1.

6) Subjects failure with autologous hematopoietic stem-cell transplantation (ASCT), anti-PD-1 or CAR-T therapy are eligible which must be more than 3 months.

7) Subjects must have adequate bone marrow, live, renal, lung and heart functions:

WBCs ≥ 2000/μL;

Absolute neutrophil count (ANC) ≥ 1500/μL;

Platelets ≥ 70 x $10^3$/μL;

Hemoglobin ≥ 7.0 g/dL;

Serum creatinine of ≤ 1.5 × ULN or creatinine clearance > 40 mL/minute;

AST ≤ 1.5 × ULN;

ALT ≤ 1.5 × ULN;

Total bilirubin ≤ 1.5 × ULN (except subjects with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL);

Myocardial enzyme ≤ 1.5 × ULN;

minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation > 91 % on room air;

No clinically significant pleural effusion.

8) No active symptomatic ischemic heart disease, myocardial infarction or congestive heart failure within the past year. Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an ECHO, and no clinically significant ECG findings.

9) Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 3 days prior to the first dose, and must not be lactating.

10) Women and men of childbearing potential must agree to use an adequate

method of contraception for the course of the study through 120 days after the last dose of investigational product.

11) Subjects must sign written informed consent in accordance with regulatory guidelines. This must be completed before the administration of protocol related procedures. The consent includes scheduled visits, treatment schedule and a series of laboratory tests.

**4.2 Exclusion criteria**

1) Subjects with a history of central nervous system involvement by PMBCL.
2) Subjects with previous or concurrent other malignancies unless a complete remission was achieved at least 3 years prior to study entry and no additional therapy is required.
3) Subjects with any autoimmune disease or history of syndrome that requires corticosteroids or immunosuppressive medications.
4) Serious uncontrolled medical disorders or active infections, pulmonary and intestinal infection especially.
5) Active alimentary tract hemorrhage or history of alimentary tract hemorrhage within 1 month.
6) CNS involvement.
7) Prior organ allograft or allogeneic bone marrow transplantation.
8) ASCT within the previous 3 months.
9) Other antitumor antibodies within 4 weeks, previous treatment with anti-PD-L1, anti-PD-L2, anti-CTLA-4 or agents targeting T-cell co-stimulation.
10) Prior radiotherapy within 6 months.
11) Positive for HIV, active hepatitis and syphilis.
12) History of Grade 4 anaphylactic to monoclonal antibody treatment, or known to be allergy to any component of SHR-1210 previously.
13) Upon the judgment by the investigator, subjects have other factors that possibly cause the halfway-termination of this study, such as other serious

illnesses (including mental illness) that require concomitant treatment, serious laboratory abnormalities, with family or social factors, which may influence the safety of the subject, or the collection of trial data and samples.

**4.3 Criteria for termination of treatment**

1) Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment. Document the reason(s) for stopping treatment.
2) A serious adverse event that requires the subject's being withdrawn from the trial. In this event, report the severe adverse events and document the reason(s) for withdrawal.
3) Objective disease progression or subjects is no longer receiving clinical benefit.
4) Severe non-compliance with the study protocol as judged by the investigator.
5) Subjects has received the maintenance regimen for 1 year and achieved persistent objective response.

**4.4 Criteria for removal from study**

Once a subject has received the treatment, subjects should be followed until the subject withdraws consent, dies or are lost to follow up. Below are examples for premature discontinuation include:

1) Rapid progression requiring alternative medical or surgical intervention.
2) Subjects lost to follow-up.
3) At any time, the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

# 5. Study design

## 5.1 Overall design

This single-arm, open-label, single-center, phase II trial was designed to assess the safety and efficacy of the combined regimen of SHR-1210 (PD-1 blockade) and GVD chemotherapy (gemcitabine, vinorelbine bitartrate and doxorubicin hydrochloride liposomal) as a salvage therapy in patients with rrPMBCL. The primary objectives are the objective response rate (ORR) and toxicity of the regimen. The secondary objectives include various efficacy parameters, complete response (CR) rate, time to response (TTR), duration of response (DOR) and progression-free survival (PFS).

This study includes the screening phase, treatment phase and follow-up phase. Baseline evaluation was performed in the screening phase, and the subjects met the eligibility criteria would process to the subsequent treatment phase.

## 5.2 Baseline evaluation

Once a subject met the initial eligibility criteria via outpatient service, they will be asked to sign of the informed consent form and obtain a subject ID. The baseline evaluation must be performed.

1) Baseline disease, treatment history and tumor assessment including formal documentation of measurable lesions should be performed within 2 weeks.
2) Hb, WBC, differential, platelets, prothrombin time, partial thromboplastin time.
3) LDH, alkaline phosphatase, bilirubin, albumin, calcium, phosphate, uric acid, BUN, creatinine, and electrolytes.
4) ECHO to assess cardiac ejection fractions as clinically indicated.
5) Electrocardiogram.
6) Pregnancy test in women of childbearing age.
7) Infection disease scteening: HIV: serology; HBV: HBsAg, Anti-HBs, HBeAg, Anti-HBc, Anti-HBe, HBV DNA $\geq 10^4$/ml, hepatocyte transaminase; HCV: HCV

antibodies and HCV RNA.

8) FDG-PET scan of whole body, and computed tomography (CT) of chest, abdomen, and pelvis.
9) Biopsy of accessible mediastinal mass or lymph node, if the clinical condition allowed, for confirmation of histological diagnosis and multiplex immunofluorescence tissue staining. Biopsy of easily accessible lymph nodes should be performed for research purposes even if the diagnosis is clearly established from submitted material. Biopsy of relatively inaccessible lymph nodes (i.e. high axillary nodes) will only be performed if needed for definitive diagnosis and not for research purposes alone.

**5.3 Studies during treatment**

1) The clinical response will be evaluated by CT every 2 cycles and FDG-PET every 4 cycles per the Lugano Response Criteria for Non-Hodgkin's Lymphoma.
2) Adverse event assessments should be documented before each cycle of treatment.
3) All of the clinical exam and biochemistry tests will be collected on Days 1 (before day-1 administration) of each cycle.
4) Peripheral blood samples (10 ml) will be collected on day 1 of each cycle (before day-1 administration) for the phenotype and activity analysis of peripheral T cells via flow cytometry.
5) Five milliliter of serum samples will be collected on day 1 (before day-1 administration) of cycle 1 and 3 for the serum cytokines and chemokines analysis.

**5.4 Treatment duration**

1) Study drug is administered via intravenous infusion on Day 1 and Day 2 of each cycle up to 12 cycles.
2) Patients achieving CR will receive 4 more cycles for a second PDG-PET confirmation.

3) The subjects, who achieve confirmed CR or obtain PR after 12 cycles of combination treatment, will receive the maintenance SHR-1210 monotherapy.
4) Early termination of the treatment of SHR-1210 plus GVD chemotherapy will allowed when disease progression, serious toxicity, withdrawal of consent.
5) The subjects with disease progression during the combination treatment will transferred to the stage 2 clinical trial of decitabine primed SHR-1210 plus GVD chemotherapy with a new informed consent.

**5.5 Studies on completion of therapy**

On completion of therapy, all initially positive or abnormal the clinical exam, biochemistry test, radiologic imaging studies will be repeated. FDG-PET should be performed. Accessible residual nodes should be biopsied for pathological analysis and multiplex immunofluorescence tissue staining. Patients who are taken off protocol will continue to be followed for survival.

**5.6 Follow-up**

1) The follow-up of safety will be performed within the first 3 months from the last cycle of treatment. Beyond 3 months, patients could be followed for ongoing drug-related events until start of another anti-tumor treatment.
2) The subjects who discontinue the study for non-progression of disease will be included in the follow-up of response duration until disease progression, lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy. Radiographic assessments will be performed every 3 months during the first follow-up year, every 6 months during the second year, every 12 months during the third year, and yearly thereafter.
3) All patients will be followed for survival every 3 months until death or withdrawal of study consent.

### 5.7 Response criteria

From the investigators review of the imaging scans, the tumor response data will be used according to the Lugano Response Criteria for Non-Hodgkin's Lymphoma recommended by National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in B-Cell Lymphomas. The Criteria could be found in Appendix. It will also be used to determine the endpoints CR rate, ORR, DOR and PFS from the overall visit response and scan data.

At each visit, subjects will be assigned a Lugano Response Criteria for Non-Hodgkin's Lymphoma visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessment. If a subject has a tumor assessment that cannot be evaluated then the subject will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

Additional imaging assessments may be performed at any time during the study when the investigator decided to support the efficacy evaluations for a subject, as necessary.

## 6. Treatment plan

### 6.1 SHR-1210 plus GVD chemotherapy treatment

The enrolled subjects will receive intravenous GVD chemotherapy (day 1) consisting of gembitabine (1000 mg/m$^2$), vinorelbine bitartrate (30 mg) and doxorubicin hydrochloride liposomal (20 mg/m$^2$) plus 200 mg SHR-1210 (day 2) every 3 weeks.

The patients with disease progression during the combined therapy will discontinued and should be considered for the stage 2 trial. The stage 2 trial is to assess the efficacy of decitabine primed SHR-1210 plus GVD chemotherapy in patients who relapsed or refractory in this clinical trial. If the patients agree to enter the stage 2 trial, a new informed consent and baseline evaluation will be required.

| Drug | Dose | Rout | Treatment Days |
|---|---|---|---|
| **Gemcitabine** | 1g/m$^2$/day | IV | 1 |
| **Vinorelbine Bitartrate** | 30 mg/day | IV | 1 |
| **Doxorubicin Hydrochloride Liposomal** | 20 mg/m$^2$/day | IV | 1 |
| **SHR-1210** | 200 mg/day | IV | 2 |
| **Next Cycle*** | | | Day 21 |

* Repeat cycles every 3 weeks (21 days).

**6.2 Dose modification**

1) Dose modification of SHR-1210 is not allowed.

2) Modification of gemcitabine, vinorelbine and doxorubicin doses was done according to the locally approved product information.

- ANC ≥ 1000/μL and platelets ≥ 50 x 10³/μL on day 21, begin treatment on time;
- ANC < 1000/μL and/or platelets < 50 x 10³/μL on day 21, hold the next dose for 1 week;
- If counts still low after 1-week delay, decrease 20% dose level of last cycle.

**6.3 Maintenance therapy**

The subjects achieving the second confirmed CR or obtaining PR after 12 doses would be followed by the maintenance SHR-1210 monotherapy.

If a patient is unable to complete all 12 cycles of SHR-1210 plus GVD chemotherapy, and the principal investigator determines that it is in the patient's best interest; the patient would advance into the maintenance SHR-1210 monotherapy.

In the maintenance phase, 200 mg of SHR-1210 was administered intravenously every 3 weeks for 4 cycles followed by every 6 weeks up to 1 year.

### 6.4 Radiation therapy allowance

The patients achieving the second confirmed CR during the treatment of SHR-1210 plus GVD chemotherapy will be allowed to received consolidated local radiotherapy, if he/she did not have a radiotherapy treatment history. These patients will remain enrolled on this study as the vehicle for the radiation treatment so that we can obtain pilot information on this treatment.

### 6.5 Concomitant treatments

1) The short or long acting granulocyte colony stimulating factor (G-CSF) can be given if the patients suffer severe neutropenia (above grade 3) and stopped 24 hours before treatment.
2) Hydration and alkalization as routine treatment during chemotherapy will be allowed.
3) Subjects are permitted the use of topical corticosteroids except intravenous medication. When adverse events happened, systemic corticosteroids are permitted in a short period of time.
4) Appropriate auxiliary drug, such as liver-protective, heart-protective and stomach-protective, are permitted to perform concomitant with investigational drugs.
5) Hormonal therapy, immunotherapy regimens or concurrent immunosuppressive agents should NOT be used as pre-medication, during treatments and following stage.
6) Anti-tumor drugs and adjuvant drugs related to tumor therapy should be discontinued during treatments, including anti-tumor traditional Chinese medicine and immunological preparations.

# 7. Investigational products

## 7.1 General information

In this protocol, investigational products are SHR-1210, gemcitabine, vinorelbine and doxorubicin. Non-investigational products used in this study was support or escape medication for preventative, diagnostic, or therapeutic reasons.

| Name | Souse | Dosage form | Rout | Specification | Storage and stability |
|---|---|---|---|---|---|
| **Gemcitabine** | Eli Lilly and Company | Lyophilized powder | IV | 1 g | Room temperature (20-25℃) |
| **Vinorelbine Bitartrate** | Pierre Fabre | Injection | IV | 10 mg:1 ml | medical refrigerator (2-8℃), away from light. |
| **Doxorubicin Hydrochloride Liposomal** | Shijiazhuang Pharm. | Injection | IV | 20mg: 10 ml | medical refrigerator (2-8℃) |
| **SHR-1210** | Shanghai Hengrui Pharm. | Lyophilized powder | IV | 200 mg | medical refrigerator (2-8℃) |

## 7.2 Drug label

The study drugs will be packaged according to current good manufacturing practice requirements. Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be provided in Chinese.

**A phase II study to investigate the safety and efficacy pf PD-1 antibody SHR-1210 plus GVD chemotherapy for relapsed/refractory PMBCL**
**ONLY FOR CLINICAL STUDIES**

Clinicaltrial ID: NCT03346642 License mumber: S2016-127-01

Indication: Primary Mediastinal Large B-cell Lymphoma

Strength: Lyophilised powder for injection, 200 mg/vial

Dosage: prepared as per the trial protocol, for intravenous injection only

Preparation date: __ __ __ __ / __ __ / __ __ Subject mumber: _____

Dose: _____mg

Cycle _____ Day _____

Storage: stored at medical refrigerator (2-8℃), away from light Batch No:

Expiry date: year 20___ month ___ day ___

Manufacture unit: Shanghai Hengrui Medicine Co., Ltd.

## Gemcitabine

**ONLY FOR CLINICAL STUDIES**

**A phase II study to investigate the safety and efficacy pf PD-1 antibody SHR-1210 plus GVD chemotherapy for relapsed/refractory PMBCL**

Manufacture unit: Eli Lilly and Company

Strength: Lyophilised powder for injection, 1 g/vial

Dosage: prepared as per the commercial package insert

Preparation date: __ __ __ __ / __ __ / __ __ Subject mumber: _____

Dose: _____mg

Cycle _____ Day _____

Expiry date: year 20___ month ___ day ___

## Vinorelbine Bitartrate

**ONLY FOR CLINICAL STUDIES**

**A phase II study to investigate the safety and efficacy pf PD-1 antibody SHR-1210 plus GVD chemotherapy for relapsed/refractory PMBCL**

Manufacture unit: Pierre Fabre Medicament Production-Aquitaine Pharm

Strength: Injection, 10 mg:1 ml

Dosage: prepared as per the commercial package insert

Preparation date: __ __ __ __ / __ __ / __ __ Subject mumber: _____

Dose: _____mg

Cycle _____ Day _____

Expiry date: year 20___ month ___ day ___

**Doxorubicin Hydrochloride Liposomal**

**ONLY FOR CLINICAL STUDIES**

**A phase II study to investigate the safety and efficacy pf PD-1 antibody SHR-1210 plus GVD chemotherapy for relapsed/refractory PMBCL**

Manufacture unit: Shijiazhuang Pharmacenutical Group (CSPS Pharm)

Strength: Lyophilised powder for injection, 1 g/vial

Dosage: prepared as per the commercial package insert

Preparation date: __ __ __ __ / __ __ / __ __ Subject mumber: _____

Dose: _____mg

Cycle _____ Day _____

Expiry date: year 20___ month ___ day ___

## 7.3 Handling and Dispensing

Management and distribution of the investigational product for this study will be performed by designated person. All the investigational products are only used for the study subjects who are included in this clinical trial. The dosage and administration method should be in accordance with the protocol. The distribution and recovery of each drug shall be recorded on a dedicated record sheet in a timely manner.

The investigational products should be stored in a secure area according to storage requirements. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

## 7.4 Preparation and administration

1) The chemotherapeutic drugs, gemcitabine, vinorelbine and doxorubicin, have been marketed. For the detailed preparation method, see the commercial package insert.
2) SHR-1210 is stored at refrigerated temperature (2-8°C). Each vial of sterile lyophilized powder shall be reconstructed in 5ml of distilled water for injection. The distilled water shall be added slowly along the wall of the vial. Do not sprinkle the distilled water directly on the surface of the lyophilized powder (40

mg / mL after reconstruction). Visually observe and ensure that the solution is clear, colorless and free from particulate matter. Any partial vials should be safely discarded per the sites standard operating procedures (SOPs) and should not be reused. SHR-1210 can be diluted in 100 ml of 5% glucose injection. The final concentration shall be maintained between 0.5 mg / ml and 10 mg / ml. Intravenous infusion shall be performed with a medical infusion pump using an infusion set with an online filter (0.2 μM) within 2 hours after dilution. The total infusion time should be less than 60 minutes, and flush the line with an adequate amount of 5% glucose injection at the end of each infusion.

# 8. Safety reporting requirements

## 8.1 Definition of adverse events (AE)

An adverse event is defined as any harmful event, reaction, side effect, or untoward occurring in a patient or clinical trial subject, a whether or not considered causally related to the investigational products. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. An AE not only includes an undesirable medical condition, but also involves run-in or washout periods, even if no study treatment has been administered in clinical studies. All the AE encountered during the study, observed by the doctor or reported by the patient, will be recorded on the case report form in the section provided for this purpose.

## 8.2 Treatment-related AE

Treatment-related AE means any adverse event for which there is a reasonable possibility that the drug caused the adverse event, which means there is evidence to suggest a causal relationship between the drug and the adverse event. This implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

### 8.3 Immune-mediated AE

SHR-1210 can result in some immune-mediated adverse events probably due to T-cell activation and proliferation. The immune-mediated AE is defined as an adverse event of unknown etiology associated with drug exposure and consistent with an immune phenomenon, and after ruling out neoplastic, infectious, metabolic, toxin or other etiologic causes.

Once the immune-mediated adverse reaction is noted, appropriate work-up should be performed, and steroid therapy may be considered if clinically necessary. However, the patient must be informed that the clinical anti-tumor responses have been maintained in patients treated with corticosteroids and discontinued from SHR-1210. The skin rash/toxicity should be treatment as ESMO Clinical Practice Guidelines, 2017.

### 8.4 Serious AE (SAE)

A SAE is an AE occurring during any study phase that meet the following criteria:

1) Results in death;

2) Is immediately life-threatening, which means the patients lie in risk of death from the AEs as it occurred or it is suspected that use or continued use of the drug would results in patients' death;

3) Requires in-patient hospitalization or prolongation of existing hospital;

4) Results in persistent or significantly disability/incapacity or disruption of the ability to conduct normal life functions;

5) Is a congenital abnormality or birth defect;

6) Is an important medical event that might need medical intervention to prevent one of the outcomes listed above.

### 8.5 Grading and recording of AEs

AEs will be collected from time of receiving the products throughout the

treatment period and including the safety follow-up period (3 months after last dose).

After this study ends, there might be some patients remaining on study treatment. For these patients will continue to collect information about AEs.

Any AE that is unresolved will be followed up by the investigators for as long as medically indicated. If any investigator learns of any SAEs, including death, at any time, and considers there is a reasonable possibility that the events, the results need document.

All events with an assigned CTCAE grades use the grading scales in the current National Cancer Institute CTCAE, version 5.0. For those events without assigned CTCAE grades, the severity of mild, moderate, severe and life-threatening, corresponding to Grades 1 - 5, as flowing:

- 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 (ADL) (refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
- Grade 3, Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4, Life-threatening consequences; urgent intervention indicated.
- Grade 5, Death related to AE.

The following variables will be collected for each AE:

| | |
|---|---|
| AEs | AE;<br>The data when the AE started and stopped;<br>Changes in CTCAE grade;<br>The serious grade of the AE;<br>Action taken with regard to investigational product;<br>Outcome;<br>Treatment measures. |
| SAEs | Date AE met criteria for SAE;<br>The cause of serious AE;<br>Date of hospitalization;<br>Date of discharge;<br>Causality assessment in relation to study procedures;<br>Description of AE. |

### 8.6 The report of deaths

All deaths during the study or within the follow-up period should be reported. If death is directly due to disease progression, it should be communicated to the study monitor at the next monitoring visit and should be documented in the case report form, but should not be reported as a SAE in the study; When death is not clearly due to disease progression or the disease under study the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should assign the primary cause of death with any contributory causes.

### 8.7 Management of the treatment related toxicities

If patients experience unacceptable toxicity, the patient should be withdrawn from the study and observed until the toxicity was resolved.

If patients show ≥ grade 3-toxicity, and the investigators consider the AE of concern to be specifically associated with investigational drugs, dosing will be interrupted and supportive therapy administered as required in accordance with guidelines.

If the toxicity resolves or reverts to ≤ grade 2 within 21 days, treatment with investigational drugs may be restarted at the same dose.

## 9. Statistical analyses

### 9.1 Statistical considerations

The detailed summary of the data collected in this study and the statistical analysis method will be prepared prior to first subject enrolled and recorded in the statistical analysis plan (SAP). If any change to the study protocol is judged by the principal investigator to have an important effect on the statistical analysis plan, the SAP needs to be re-modified as to keep consistency with the study protocol.

The primary objective of this trial is to determine safety and ORR with a minimal follow-up of 6 months, the data cutoff will take place 6 months after the last

subject enrolled. At this time, safety, time to response and response duration rate at 6 months will also be summarized. The secondary objective is further analysis of the efficacy parameters, including PFS, OS and DOR, and the long-term survival data will be reported at least 12 months after the last subjects has been enrolled.

All the subjects who have taken at least one dose of the investigational products will be considered as the **safety- assessable population**. All the subjects enrolled who have taken at least two dose of the investigational product and received at least one evaluable post-treatment tumor scan will be accepted as the **efficacy-evaluable population**.

### 9.2 Sample size determination

A'Hern Single-Stage phase 2 design was used to determine the sample size of this clinical trial of SHR-1210 plus GVD chemotherapy. According to the previously reported data, the ORR of PD-1 blockade monotherapy for the patients with relapsed//refractory PMBCL is about 40%. Based on this, we set the null hypothesis of a proportion of patients with an objective response of 40% or lower versus the alternative hypothesis that it was 70% or higher. At least 25 patients would need to be enrolled with a two-sided significant level of 0.05 and 90% power.

### 9.3 Outcome assessment

**1) Objective Response Rate (ORR) and Complete Remission (CR) Rate**

ORR is defined as the proportion of patients with at least one visit response of CR or PR that is confirmed at least 6 weeks later. CR rate is defined as the proportion of patients whose best clinical response is CR. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of objective response. A CR evaluation should be confirmed by PET-CT assessment. However, any CR or PR that occurred after a further anticancer therapy will not be included in ORR analysis.

**2) Duration of Response (DOR)**

DOR is defined as the time from the date of first documented response that is subsequently confirmed until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If the disease does not progress after a response, their duration of response will use the PFS censoring time.

**3) Time to Response (TTR)**

TTR is defined as the period from the date of first dose to the date of the first evaluated response of CR or PR. If the response is not confirmed, it will not be included.

**4) Tumor Shrinkage**

Tumor shrinkage is assessed using lymphoma response. The SPD (sum of the product of the diameters) change and percentage change from baseline in sum of tumor size at each assessment will be calculated. The best change in tumor size will include all assessment prior to progression or start of subsequent anticancer therapy.

**5) Progression-free survival (PFS)**

PFS is defined as the time of first dosing to the date of disease progression or death (by any cause in the absence of progression). Subjects who are alive without disease progression or lost to follow-up are censored. Patients quit the study due to toxicity and without disease progression, had PFS censored at the time of last radiological scan assessment.

**6) Overall Survival**

Overall survival is defined as the time from the data of first dose until death due to any cause. Any patient unknown to have died at the time of analysis will be censored based on the last record date on which the patient was known to be alive.

### 9.4 Safety assessment

Adverse events will be listed individually by patient. Any AE occurring within 3 months of discontinuation of investigational product will be including in the AE summaries. For change from baseline summaries for vital signs, laboratory data and

physical examination, the baseline value will be the latest result obtained prior to the start of investigational product. The denominator in vital signs data should include only those patients with recorded data, and in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality.

**9.5 Tumor PD-L1 assessment**

The baseline tumor samples will be obtained by excisional biopsy or with a core needle, followed by formalin fixation and paraffin embedding. The confirmation of histological diagnosis and tumor PD-L1 expression will be detected by the classical immunohistochemical pathological analysis. Extra biopsy samples will be utilized to confirmed the tumor PD-L1 expression by Multiplex immunofluorescence tissue staining as followed.

Slides were deparaffinised in xylene and rehydrated in a series of graded alcohols. Antigen retrievals were performed in citrate buffer (pH6) with a microwave (Sharp, R-331ZX) for 20 min at 95°C followed by a 20 min cool down at room temperature. After the quenching of endogenous peroxidase in 3% $H_2O_2$, slides were incubated with blocking reagent (ZSGB-BIO, ZLI-9022) for 30 min at room temperature. Antigens were then successively detected using the Opal protocol. Briefly, each primary antibody was incubated for 2 hr in a humidified chamber at 37°C, followed by detection using the horseradish peroxidase (HRP)-conjugated secondary antibody (GBI Labs, Polink-1 HRP polymer detection kit) and TSA-fluorophores (PerkinElmer, Opal 7-color IHC Kit, NEL797001KT, 1:100, 20-60 sec), after which the primary and secondary antibodies were thoroughly eliminated by heating the slides in citrate buffer (pH 6.0) for 10 min at 95°C using microwave. In a serial fashion, each antigen was labeled by distinct fluorophores. Nuclei were subsequently visualized with DAPI (1:2000), and the slides were coverslipped using ProLong Gold Antifade Mountant (ThermoFisher, P36934). Using this Opal protocol, CD20 (Abcam, ab9475, 1:200, Opal690), PD-L1 (WuXi Diagnostics,

2130WPI1A02A, Opal620), PD-1 (CST, 43248, 1:100, Opal520), CD3 (Abcam, ab16669, 1:200, N430) were sequentially detected within sample sections.

For each patient sample, 5-10 fields of view were acquired at 20 × resolution as multispectral images by using the Vectra Polaris (PerkinElmer), depending on tumor size. After image capture, each field of view was spectrally unmixed, cell segmentation and cell quantitation using the in Form Advanced Image Analysis Software (PerkinElmer) version 2.4.

**9.6 Peripheral blood T cell and serum cytokine/chemokine assessment**

Blood samples will be collected for peripheral T cell assessment on the first day prior administration of the first five treatment cycles (Cnd0, n indicates 1 to 5). The peripheral blood was collected in sodium heparin anticoagulant vacutainer tubes. Briefly, 100 μl of the anticoagulant peripheral blood was incubated with antibodies specific to cell-surface antigens expressed on T lymphocytes. After red blood cell lysis and washing, the cells were detected on a BD FACSCalibur flow cytometer (BD Biosciences). The following antibodies were used to detect surface marker expression and obtained from BD Biosciences: anti-CD3-PerCP (347344), anti-HLA-DR (559866) and isotype-matched antibodies. For the intracellular cytokine expression, blood cells were stimulated with T cell stimulation cocktail (including PMA, Ionomycin and transport inhibitors, eBioscience, 00-4975-93) for 4 h of incubation, and cells were stained with anti-CD3 and permeabilized before the addition of anti-IFN-γ (554700). Stained cells were detected by flow cytometry using FACSCalibur flow cytometer (BD Biosciences) to collect a minimum of 10,000 CD3+ lymphocytes.

Serum samples will be collected for cytokines and chemokines analysis on the first day prior administration of both the first and third treatment cycles. The detected cytokines and chemokines include IL-1β、2、 4、6、8 (CXCL8)、10、12p70、17A、18、23、33, IFN-α2, IFN-γ, TNF-α, soluble Fas (sFas), soluble FasL (sFasL), granzyme A, granzyme B, perforin, granulysin, MCP-1 (CCL2). The analysis was

performed using 200 μl serum of each sample via LEGENDplex™ bead-based immunoassays (Biolegend, LEGENDplex™ Human Inflammation Panel [740808], LEGENDplex™ Human CD8/NK Panel [740267]).

**9.7 Data analysis**

Appropriate descriptive statistics will be used for all variables. Continuous variables will be summarized by mean, standard deviation, median, maximum and minimum. Categorical variable will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the full analysis set.

CR rate and ORR will be presented together with two-sided 95% exact confidence interval (CI), which is calculated using the Wilson method. Summaries of the number and percentage of patients with best response in each of the follow categories will be summarized: complete remission (CR), partial response (PR), stable disease (SD), progressive disease (PD) and not evaluable (NE).

Duration of response in responding subjects will be summarized and the number of responding subjects with a duration of response >6, >12, >18 and >24 months will be presented. A Kaplan Meier plot and median duration of response with 95% CI will be presented.

The best absolute change in target lesion tumor size from baseline and percentage change in target lesion tumor size from baseline will be summarized using descriptive statistics and presented at each time point.

PFS will be displayed using a Kaplan-Meier plot. The number events, median, and the proportion of patients without an event at 6, 12 and 24 months summarized.

When there is sufficient data, OS will be displayed using a Kaplan-Meier plot. The number events, median, and the proportion of patients without an event at 1, 2, or 3, 4, 5 years will be summarized. Its is should be appropriate, summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up and have withdrawn consent will be presented.

## List of abbreviations

| Abbreviation | Full name |
|---|---|
| ADL | Activities of Daily Living |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ASCT | autologous stem-cell transplantation |
| AST | aspartate aminotransferase |
| BUN | blood urea nitrogen |
| BV | brentuximab vedotin |
| CAR-T | Chimeric antigen receptor T cell |
| CI | confidence interval |
| CR | complete response |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTLA-4 | Cytotoxic T lymphocyte-associated antigen 4 |
| DLBCL | diffuse large B-cell lymphoma |
| DOR | duration of response |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ESMO | European Society for Medical Oncology |
| FACS | fluorescence activated cell sorting |
| FDA | Food and Drug Administration |
| FDG-PET | 18F-fluorodeoxyglucose–position-emission tomography |
| G-CSF | granulocyte colony stimulating factor |
| GVD | gembitabine, vinorelbine and doxorubicin |
| Hb | hemoglobin |
| HBV | hepatitis B virus |
| HCG | human chorionic gonadotropin |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HL | Hodgkin’s lymphoma |

| | |
|---|---|
| HPR | horseradish peroxidase |
| IRB | Institutional Review Board |
| IV | intravenous |
| JAK2 | Janus kinase 2 |
| LDH | lactate dehydrogenase |
| MDSCs | myeloid-derived suppressor cells |
| NCI | National Cancer Institute |
| NE | not evaluable |
| nHL | non-Hodgkin lymphomas |
| nsHL | nodular sclerosis Hodgkin's lymphoma |
| ORR | objective response |
| OS | overall survival |
| PD | progression disease |
| PD-1 | Programmed death-1 |
| PD-L1 | Programmed death ligand 1 |
| PD-L2 | Programmed death ligand 2 |
| PFS | progression-free survival |
| PMBCL | Primary Mediastinal B-cell Lymphoma |
| PR | partial response |
| rrPMBCL | relapsed/refractory Primary Mediastinal B-cell Lymphoma |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | stable disease |
| SOPs | standard operating procedures |
| SPD | sum of the product of the diameters |
| STAT | signal transducer and activator of transcription |
| TTR | time to response |
| ULN | upper limit of normal |
| WBC | white blood cell |

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# Appendix 1. Time and event schema

| | Baseline | Each cycle | Follow-up | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit name | V0 | | V7 | V8 | V9 | V10 | V11 | V12 | V13 | V14 | V15 | V16 |
| Week | -2 to -1 | | 36±3 | 48±3 | 72±3 | 96±3 | 120±7 | 144±7 | 168±7 | 192±7 | 216±7 | 240±7 |
| Month | | | 9 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 |
| Inform consent | √ | | | | | | | | | | | |
| Demography | √ | | | | | | | | | | | |
| Clinical history | √ | | | | | | | | | | | |
| Pathologic result conformation | √ | | | | | | | | | | | |
| Signs of life | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Physical examination | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| General information | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| IHC | √ | | √ | | | | | | | | | |
| ECOG | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Blood cell count | √ | | | | | | | | | | | |
| Urine routine | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Stool routine | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Renal/Liver function | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| HCG | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Coagulation function | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Infectious disease screening | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Immune function | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Laboratory assessments | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| ECG | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| ECHO | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| CT | √ | Every 2 cycles | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| FDG-PET-CT | √ | Every 4 cycles | √ | | √ | | √ | | √ | | √ | |
| Tumor biobsy | √ | | √ | | | | | | | | | |
| PMBC collection | √ | First 5 cycles | | | | | | | | | | |
| Serum collection | √ | Cycle 1 and 3 | | | | | | | | | | |
| AE evaluation | | √ | √ | √ | | | | | | | | |

# Appendix 2. Lymphoma response criteria

## 1. LUGANO RESPONSE CRITERIA FOR NON-HODGKIN'S LYMPHOMA

| Response | Site | PET-CT (Metabolic response) | CT (Radiologic response)[d] |
|---|---|---|---|
| **Complete response** | Lymph nodes and extralymphatic sites | Score 1, 2, 3[a] with or without a residual mass on 5 point scale (5-PS)[b,c] | All of the following:<br>Target nodes/nodal masses must regress to ≤1.5 cm in longest transverse diameter of a lesion (LDi) No extralymphatic sites of disease |
| | Non-measured lesion | Not applicable | Absent |
| | Organ enlargement | Not applicable | Regress to normal |
| | New Lesions | None | None |
| | Bone marrow | No evidence of FDG-avid disease in marrow | Normal by morphology; if indeterminatem and flow cytometry IHC negative |
| **Partial response** | Lymph nodes and extralymphatic sites | Score 4 or 5[b] with reduced uptake compared with baseline. No new progressive lesions.<br>At interim these findings suggest responding disease. At end of treatment these findings may indicate residual disease. | All of the following:<br>≥ 50% decrease in SPD of up to 6 target measureable<br>nodes and extranodal sites<br>When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value.<br>When no longer visible, 0x0 mm<br>For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation |
| | Non-measured lesion | Not applicable | Absent/normal, regressed, but no increase |
| | Organ enlargement | Not applicable | Spleen must have regressed by >50% in length beyond<br>normal |
| | New Lesions | None | None |
| | Bone Marrow | Residual uptake higher than update in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the content of a nodal response, consider further evaluation with biopsy, or an interval scan. | Not applicable |

| Response | Site | PET-CT (Metabolic response) | CT (Radiologic response)[d] |
|---|---|---|---|
| **No response or stable disease** | Target nodes/ nodal masses, extranodal lesions | Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment. No new or progressive lesions. | < 50% decrease from baseline in SPD of up to 6 dominant, measureable nodes and extranodal sites; no criteria for progressive disease are met |
| | Non-measured lesion | Not applicable | No increase consistent with progression |
| | Organ enlargement | Not applicable | No increase consistent with progression |
| | New Lesions | None | None |
| | Bone marrow | No change from baseline | Not applicable |
| **Progressive disease** | Individual target nodes/ nodal masses, extranodal lesions | Score 4 or 5[b] with an increase in intensity of uptake from baseline<br>and/or<br>New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment[e] | Requires at least one of the following PPD progression:<br>An individual node/lesion must be abnormal with:<br>LDi > 1.5 cm and<br>Increase by ≥ 50% from PPD nadir and<br>An increase in LDi or SDi from nadir<br>0.5 cm for lesions ≤ 2 cm<br>1.0 cm for lesions > 2 cm<br>In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline<br>New or recurrent splenomegaly |
| | Non-measured lesion | None | New or clear progression of preexisting nonmeasured lesions |
| | New Lesions | New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered[e] | Regrowth of previously resolved lesions A new node > 1.5 cm in any axis<br>A new extranodal site > 1.0 cm in any axis; if < 1 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma<br>Assessable disease of any size unequivocally attributable to lymphoma |
| | Bone Marrow | New or recurrent FDG-avid foci | New or recurrent involvement |

[a] Score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de- escalation is investigated, it may be preferable to consider score 3 as an inadequate response (to avoid under-treatment).

[b] See PET Five Point Scale (5-PS).

[c] It is recognized that in Waldeyer's ring or extranodal sites with high physiological uptake or with activation within spleen or marrow, e.g. with chemotherapy or myeloid colony stimulating factors, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiological uptake.

[d] FDG-avid lymphomas should have response assessed by PET-CT. Diseases that can typically be followed with CT alone include CLL/SLL and marginal zone lymphomas.

[e] False-positive PET scans may be observed related to infectious or inflammatory conditions. Biopsy of affected sites remains the gold standard for confirming new or persistent disease at end of therapy.

SPD – Sum of the product of the perpendicular diameters for multiple lesions; LDi – Longest transverse diameter of a lesion; SDi – Shortest axis perpendicular to the LDi; PPD – Cross product of the LDi and perpendicular diameter

**PET Five Point Scale (5-PS)**

1 No uptake above background

2 Uptake ≤ mediastinum

3 Uptake > mediastinum but ≤ liver

4 Uptake moderately > liver

5 Uptake markedly higher than liver and/or new lesions

X New areas of uptake unlikely to be related to lymphoma

**Measured dominant lesions**

Up to 6 of the largest dominant nodes, nodal masses and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body, and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs, e.g., liver, spleen, kidneys, lungs, etc, gastrointestinal involvement, cutaneous lesions of those noted on palpation.

**Non-measured lesions**

Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant, measurable or which do not meet the requirements for measurability, but are still considered abnormal. As well as truly assessable disease which is any site of suspected disease that would be difficult to follow quantitiatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses and other lesions that cannot be confirmed and followed by imaging.

## Appendix 3. Summary of the objective response status calculation

| Target lesions | Non-target lesions | New lesions | Objective response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not evaluated | No | PR |
| SD | Non-PD or not evaluated | No | SD |
| Not evaluated | Non-PD | No | Not evaluated |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

Time point response: patients with target (+/-) non-target disease

## Appendix 4. Common terminology criteria for adverse events (CTCAE), v5.0

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

## Appendix 5. ECOG performance status scale

| Grade | Description |
|---|---|
| **0** | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| **1** | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). |
| **2** | In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| **3** | In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| **4** | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| **5** | Dead. |

## Appendix 6. New York heart association (NYHA) classification

**Class I:** patients with no limitation of activities; they suffer no symptoms from ordinary activities.

**Class II:** patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

**Class III:** patients with marked limitation of activity; they are comfortable only at rest.

**Class IV:** patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.