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Clinical Study Protocol

A Phase II Clinical Trial to Evaluate the Efficacy and Safety of Genolimzumab Injection in the Treatment of Chinese Patients with Relapsed or Refractory B-cell Non-Hodgkin Lymphoma (B-NHL)

Investigational Drug:	Genolimzumab injection (recombinant humanized anti-PD-1 monoclonal antibody injection) [GB226]
Protocol No.:	Gxplore-003
Study Phase:	Phase II
Current Protocol Version No.:	1.4
Current Protocol Version Date:	March 1, 2019
Original Protocol Version No ./Version Date	1.3/September 25, 2018
Sponsor	Genor Biopharma Co. Ltd. Huiyang Cheng Address: No. 1690, Zhangheng Road, Zhangjiang, Pudong District, Shanghai Post Code: 201203

The implementation of the trial should comply with the study protocol, *Good Clinical Practice* (ICH-GCP), and other regulatory requirements (including archiving of important documents).

Confidential Information

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PROTOCOL SYNOPSIS

Protocol number	**Gxplore-003**
Study title	A Phase II Clinical Trial to Evaluate the Efficacy and Safety of Genolimzumab Injection in the Treatment of Chinese Patients with Relapsed or Refractory B-cell Non-Hodgkin Lymphoma (B-NHL)
Sponsor	Genor Biopharma Co. Ltd.
Trial phase	Phase II
Trial sites	40 sites planned
Number of subjects	53 patients with relapsed or refractory primary mediastinal large B-cell lymphoma (rr PMBCL)
Trial objectives	Primary objective: • To evaluate the overall response rate (ORR) of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma. Secondary objectives: • To evaluate the duration of response (DOR) of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma; • To evaluate the time to response (TTR) of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma; • To evaluate the disease control rate (DCR) of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma; • To evaluate the progression-free survival (PFS) and overall survival (OS) of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma; • To evaluate the safety of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma; • To evaluate the immunogenicity of GB226. Exploratory objectives: • To explore the correlation between programmed cell death protein ligand-1 (PD-L1), programmed cell death protein ligand-2 (PD-L2), and biomarkers such as deficient mismatch repair genes (dMMR) and/or microsatellite instability (MSI) and tumor mutation burden (TMB) in the tumor tissues of patients with relapsed or refractory primary mediastinal large B-cell lymphoma and the efficacy of GB226; • To explore the correlation between immune cell typing and counting (B lymphocytes [CD19+], T lymphocytes [CD3+] and its subtypes [CD4+ and CD8+ T cells], NK/T cells [CD16+ and CD56+]) and cytokines (IL-2, IL-6, IL-8, TNFα and INFγ) and efficacy.
Trial design	This is a multi-center, prospective, open-label, single-arm phase II clinical trial to evaluate the efficacy and safety of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma, and to assess the immunogenicity of GB226. The trial plans to enroll 53 patients with relapsed or refractory primary mediastinal large B-cell lymphoma in 40 trial sites in China. The trial includes 3 periods: a screening period, a treatment period and a follow-up period. After the subjects sign the informed consent form (ICF), they will enter the screening period of up to 28 days, during which the subjects will complete the screening assessments according to the visit plan in the Schedule of Activities (Table 1). The eligible

	subjects will receive GB226 treatment at a dose of 3 mg/kg/time by intravenous infusion, once every two weeks, until confirmed progressive disease (PD), intolerable toxicity, withdrawal of informed consent, start of other anti-tumor treatment, loss to follow-up or death, treatment discontinuation at the discretion of the investigator or subject, or end of the trial. Each subject will be treated with GB226 every 2 weeks (±3 days) during the treatment period; an efficacy assessment visit will be conducted every 6 weeks (±7 days) in the first year, and every 12 weeks (±7 days) in the second year and thereafter (the interval between the first efficacy evaluation and the first administration of the investigational drug must be ≥6 weeks, except for circumstances where progressive disease is considered). If a subject who has received GB226 treatment at least once decides to discontinue the investigational drug for any reason, the subject should complete the end of treatment visit as soon as possible within 14 days after deciding to discontinue the treatment (the examination results after the last treatment within the past 14 days are acceptable). Subjects who have received GB226 treatment at least once need to undergo a safety follow-up at 30 days (±7 days) after the last administration or before starting a new anti-tumor treatment (if this follow-up overlaps with the end of treatment visit, there is no need to repeat the examinations), whichever occurs first. If a new anti-tumor treatment has not been started, the subject should complete a safety follow-up again at 90 days (±7 days) after the last administration where possible. If a subject has discontinued treatment and his/her imaging evaluation has not yet reached PD, the subject still needs to be followed up for progressive disease once every 6 weeks (±7 days) in the first year, and every 12 weeks (±7 days) in the second year and thereafter until PD (imaging evaluation), start of a new anti-tumor treatment, death or loss to follow-up. After the last safety follow-up or the last progressive disease follow-up (whichever occurs later), a survival follow-up should be performed every 3 months (±7 days) until the end of the study, death or loss to follow-up (for those without safety follow-up, the time should be counted from the last visit) to collect the subjects' subsequent anti-tumor treatment and survival status information. It is allowed to complete such follow-ups by telephone. More and more evidences show that the objective response to immunotherapy may be delayed by several weeks or months, and before that, there may be evident imaging progression or new lesions or some lesions increasing while some target lesions shrinking. After it is preliminarily assessed as progressive disease by the investigator based on the Lugano 2014 criteria, if the subject is considered to clinically benefit and tolerant to the Investigational drug, the subject is allowed to continue to receive treatment until confirmed progressive disease occurs and the investigator judges that there is no clinical benefit. Then the subject must discontinue the study treatment. The end of the trial is defined as that the last subject withdraws the informed consent, discontinues the treatment or withdraws from the trial, is lost to follow-up or dies, the treatment has been completed for 2 years, or the study ends early, whichever occurs first. The trial may end early at any time due to any reason from the sponsor. If necessary, the patient needs to conduct an end of treatment visit as soon as possible. Refer to the flow chart for specific assessments. The investigator is responsible for notifying the Ethics Committee of the institution. Schedule of Activities:

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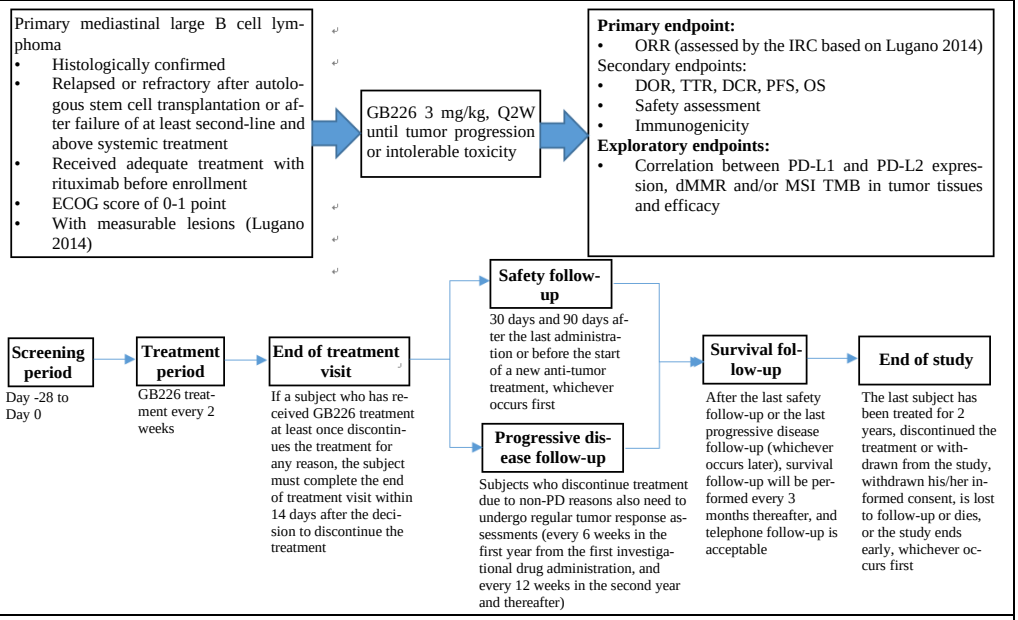

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<td>Trial population</td>
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Patients with relapsed or refractory primary mediastinal large B-cell lymphoma (rr PMBCL), defined as patients with relapsed or refractory PMBCL who have undergone autologous stem cell transplantation or have failed to respond to at least second-line and above systemic treatment. (Relapsed is defined as progressive disease after the tumor has achieved a response following the last systemic treatment; refractory is defined as the tumor failing to achieve CR or PR after the last systemic treatment)
<u>Inclusion criteria:</u>
Only those who meet all the following criteria can be included in this trial.
1. Aged ≥ 18 years, male or female;
2. Understand the trial procedures and content, and voluntarily sign a written informed consent form;
3. Histopathologically confirmed primary mediastinal large B-cell lymphoma (PMBCL):
 1) Recurrence after autologous hematopoietic stem cell transplant (ASCT), or failure to achieve CR or PR within 60 days after ASCT. If relapsed or refractory patients have received other interventions after ASCT, the disease must become relapsed or refractory after the last systemic treatment; or:
 2) Patients who are not suitable for ASCT must become relapsed or refractory after failure of second-line or above systemic chemotherapy. Local radiotherapy is not considered as a separate first-line treatment;
 3) Before enrollment, the subjects have received adequate treatment with rituximab;
4. Agree to provide archived tumor tissue specimens or fresh tissue samples;
5. ECOG score of 0-1 point;
6. Expected survival ≥ 3 months;
7. The computed tomography scan performed within 28 days before the investigational drug administration should show that there is at least one clearly measurable tumor lesion in two vertical directions (the longest diameter of intranodal lesions >1.5 cm, and the longest diameter of extranodal lesions >1.0 cm (based on the Lugano 2014 criteria);
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	8. Blood routine requires hemoglobin ≥80 g/L, neutrophils ≥1.0 $\times 10^9$/L, platelets ≥75$\times 10^9$/L (no blood transfusion or use of biological stimulating factors within 14 days before the test); 9. Serum creatinine ≤ 1.5 × ULN or calculated value of creatinine clearance ≥ 50 mL/min (Cockcroft-Gault formula); 10. Total bilirubin ≤1.5 × ULN [for patients with Gilbert syndrome, ≤5 × ULN], aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN (for patients with liver metastases, AST and/or ALT ≤ 5 × ULN); 11. Thyroid function parameters: thyroid-stimulating hormone (TSH) and free thyroxine (FT3/FT4) are in the normal range; if TSH and FT3 are not in the normal range, subjects with FT4 in the normal range can be included; 12. Females who are confirmed to be not pregnant within 7 days before administration; fertile males or females agree to take medically approved effective contraceptive measures during the entire trial period and within 6 months after the end of the trial; 13. Patients can be followed up on schedule, can communicate well with the investigator, and can complete the trial in accordance with the trial procedures. **Exclusion criteria:** Those who meet one of the following conditions will not be included in this trial. 1. Patients who have previously suffered from other malignancies (except for cured cervical carcinoma in situ and skin basal cell carcinoma or squamous cell carcinoma) shall not participate in the trial unless he/she has had a complete response for at least 5 years before enrollment and is not expected to require any other treatment during the entire trial period; 2. Confirmed lymphoma central nervous system (CNS) infiltration, including brain parenchyma, meningeal invasion, or spinal cord compression etc.; 3. Those who have received systemic chemotherapy or targeted therapy within 2 weeks before the investigational drug administration, or received radical/extensive radiotherapy, anti-tumor biotherapy (tumor vaccine, cytokine or growth factor for the purpose of tumor control) within 4 weeks, or local palliative radiotherapy within 1 week; 4. Those who have received systemically administered corticosteroids (prednisone > 10 mg/day or equivalent dose) within 2 weeks before the investigational drug administration; 5. Those who have undergone autologous hematopoietic stem cell transplantation within 2 months, or allogeneic hematopoietic stem cell transplantation within 5 years before the investigational drug administration; 6. Those who have undergone major surgery under general anesthesia within 4 weeks before the investigational drug administration; or local anesthesia/epidural anesthesia within 2 weeks; 7. Those with a history of active and known autoimmune diseases, including but not limited to systemic lupus erythematosus, psoriasis, rheumatoid arthritis, inflammatory bowel disease, and Hashimoto's thyroiditis, except for type I diabetes, hypothyroidism that can be controlled only by hormone replacement therapy, skin diseases requiring no systemic treatment (e.g., vitiligo, psoriasis), controlled celiac disease, or diseases that are not expected to recur without external stimuli; 8. Uncontrolled hypertension (systolic blood pressure> 140 mmHg and/or diastolic blood pressure> 90 mmHg) or pulmonary hypertension or unstable angina pectoris; myocardial infarction or bypass or stent surgery within 6 months before administra-

	tion; a history of New York Heart Association (NYHA) Class 3-4 chronic heart failure; clinically significant valvular disease; severe arrhythmia requiring treatment, including QTc interval ≥450 ms for males and ≥470 ms for females (calculated by Fridericia formula); left ventricular ejection fraction (LVEF) < 50%; cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months before administration; 9. Those complicated with other serious medical diseases, including but not limited to: uncontrolled diabetes, active peptic ulcer, active bleeding, etc.; 10. Those with active infections requiring systemic treatment; 11. Those with past or current active tuberculosis infection; 12. Those who are positive for human immunodeficiency virus antibody (HIV-Ab) and Treponema pallidum antibody (TP-Ab); positive for hepatitis C antibody (HCV-Ab), with hepatitis C virus RNA quantification > the upper limit of normal of the detection unit; positive for hepatitis B virus surface antigen (HBsAg), with hepatitis B virus DNA quantification > the upper limit of normal of the detection unit; 13. Comorbidities that require immunosuppressive therapy, or comorbidities that require systemic treatment at an immunosuppressive dose (prednisone> 10 mg/day or equivalent dose of similar drugs); in the absence of active autoimmune diseases, the inhaled or topical use of steroids or prednisone at a dose > 10 mg/day or equivalent doses of similar drugs is allowed; 14. Adverse reactions caused by previous treatments have not recovered to grade 1 or below (CTCAE V5.0) before medication (except for alopecia and grade 2 neurotoxicity caused by chemotherapeutic drugs); 15. Uncontrollable or significantly symptomatic pleural and abdominal effusion or pericardial effusion; 16. Those who have previously used anti-PD-1 antibody, anti-PD-L1 antibody, anti-PD-L2 antibody or anti-CTLA-4 antibody therapy (or any other antibody that acts on T cell co-stimulation or checkpoint pathways); 17. Those who have used other investigational drugs or investigational devices within 30 days before starting the use of the investigational drug; 18. Those who have used live vaccines or attenuated vaccines within 4 weeks before the investigational drug administration; 19. Those who have a history of drug addiction or drug abuse upon inquiry; 20. Those who have a history of interstitial lung disease; 21. Women who are breastfeeding and unwilling to stop breastfeeding; 22. Known to be allergic to recombinant humanized PD-1 monoclonal antibody or any of its excipients; known to have a history of allergic diseases or be of severe allergic constitution; 23. Patients with insufficient communication, understanding, and cooperation, or poor compliance, who cannot guarantee that they will proceed according to the requirements of the protocol; 24. Those who are considered by the investigator to be unsuitable for participating in this clinical trial due to various other reasons.
Investigational drug and method	The GB226 preparation is a colorless to light yellow liquid with a strength of 70 mg/7 ml/vial. GB226 is formulated in 0.9% sodium chloride solution. The concentration of administration must be strictly controlled within 1 mg/ml~10 mg/ml. The first infusion

of administration	should be completed within 60 minutes (±10 minutes); if there are no infusion-related adverse reactions, the follow-up infusions can be shortened to 30 minutes (±10 minutes). The dose of GB226 is 3 mg/kg/time, once every 2 weeks (±3 days), until confirmed progressive disease, intolerable toxicity, withdrawal of informed consent, start of other anti-tumor treatment, loss to follow-up or death, treatment discontinuation at the discretion of the investigator or subject, or end of the trial. Please refer to Section 5 for specific medication rules.
Trial endpoints	**Primary endpoint:** • The overall response rate (ORR) evaluated by the Independent Review Committee (IRC) based on the Lugano 2014 criteria refers to the proportion of subjects who have achieved complete response (CR) or partial response (PR) through imaging evaluation. The first CR or PR should be confirmed after at least 4 weeks. **Secondary endpoints:** • Duration of response (DOR) • Time to response (TTR) • Disease control rate (DCR) • Progression-free survival (PFS) • Overall survival (OS) • Safety assessments include the incidence and severity of adverse events (AE) and serious adverse events (SAE), as well as changes in laboratory test results, physical examination, electrocardiogram, and vital signs compared with baseline values. • Immunogenicity of GB226: the number and percentage of patients who develop anti-GB226 antibodies (ADA). **Exploratory endpoints:** • The expression levels of programmed cell death protein ligand-1 (PD-L1) and programmed cell death protein ligand-2 (PD-L2), and the quantitative values (cut-off value) of deficient mismatch repair genes (dMMR) and/or microsatellite instability (MSI) and tumor mutation burden (TMB); • Immune cell typing and counting (B lymphocytes [B lymphocytes [CD19+], T lymphocytes [CD3+] and its subtypes [CD4+ and CD8+ T cells], NK/T cells [CD16+ and CD56+]), and levels of cytokines (IL-2 , IL-6, IL-8, TNFα and INFγ).
Safety evaluation	From the signing of the ICF to 90 days after the last administration of GB226, the subjects will be monitored for serious adverse events and adverse events, as well as laboratory tests (including blood routine, urine routine, stood routine, clinical biochemistry, thyroid function), physical examination, vital signs, and ECG to evaluate the safety of the investigational drug. Adverse events and serious adverse events related to the investigational drug should still be collected 90 days after the end of the last GB226 administration. Adverse events during the study period need to be followed up until the event is resolved, such as recovered, return to baseline, stabilization, or the subject withdraws the informed consent, is lost to follow-up, or dies.
Concomitant treatments	Concomitant treatments include prescription drugs or over-the-counter drugs used in the period from 28 days before the first investigational drug administration to 90 days (±7 days) after the last administration or before the start of a new anti-tumor treatment (whichever occurs first). All concomitant medications should be recorded in the electronic case report form (eCRF). During the study period, patients need to be given the best supportive treatment, except for the prohibited medications specified in Section 5.5.2 of this protocol.

Sample size calculation	The primary endpoint of this study is the overall response rate (ORR) of the study treatment in patients with relapsed or refractory PMBCL. For patients with relapsed or refractory PMBCL who have undergone autologous stem cell transplantation or who have failed to respond to at least second-line or above systemic treatment, ORR >25% is considered to have clinically significant anti-tumor activity. It is expected that the ORR of GB226 in this population can reach 45%, and the following efficacy hypothesis test is performed at the level of one-sided $\alpha = 0.025$: H_0: ORR ≤25% vs. H_a: ORR> 25%, 42 subjects can provide a > 80% power to detect the efficacy; when the observed ORR is 45%, the two-sided 95% exact confidence interval given by 42 subjects is [29.6%, 61.1%]. Given a dropout rate of about 20%, the study plans to enroll 53 patients with relapsed or refractory PMBCL.
Statistical analysis methods	Statistical analysis will be performed using SAS V9.4. Descriptive statistical methods will be used to summarize the baseline characteristics, treatment status, and drug safety characteristics of the patients. Measurement data will be described by the number of cases, missing, mean, standard deviation, maximum, minimum, and median; count data will be described by the frequency table and percentage. The primary analysis of the study is to assess the ORR of GB226 in patients with relapsed or refractory PMBCL, and perform the exact test of the following superiority hypothesis on the ORR at the one-sided $\alpha = 0.025$: H_0: ORR ≤25% vs. Ha: ORR＞25%; The Clopper-pearson method will be used to give an estimate of ORR and a 95% confidence interval. If the lower limit of the interval is greater than 25%, the test is considered to be successful, and the efficacy of GB226 in patients with relapsed or refractory PMBCL will be considered as clinically significant. In addition, the secondary efficacy endpoints, including duration of response (DOR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) will be analyzed by using descriptive statistical methods. The Clopper-pearson method will be used to estimate ORR and DCR, and provide the corresponding 95% confidence intervals. The Kaplan-Meier method will be used to analyze DOR, TTR, PFS and OS, and provide the medians and 95% confidence intervals. Cut-off time for primary data analysis: It is planned to be carried out after the completion of two efficacy assessments of the last subject, or in the following situations: progressive disease, start of subsequent anti-tumor treatment, death or loss to follow-up, subject withdrawal of informed consent or discontinuation of treatment, whichever occurs first.

Table 1Schedule of Activities

	Screening period[1]	**Treatment period**											**Follow-up period**		
Time (week)		**Week 1**	**Week 3**	**Week 5**	**Week 7**	**Week 9**	**Week 11**	**Week 13**	**Week 15**	**Week 17**	**Week n**	**Treatment termination**[2]	**Safety follow-up**[3]	**Progressive disease follow-up**[4]	**Survival follow-up**[5]
Time (Day)	**Day -28 to Day 0**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day n**	**End of treatment visit**	**Day 30 and Day 90 after the last dose**	**Once every 6 weeks/every 12 weeks**	**Once every 3 months**
Time window (day)			**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**		**± 7 days**	**± 7 days**	**± 7 days**
Signing of informed consent form	X														
Evaluation of inclusion/exclusion criteria	X														
Pathological reconfirmation[6]	X														
Previous anti-tumor treatment	X														
Concomitant medications and treatments	X	X	X	X	X	X	X	X	X	X	X	X	X		
Height/weight[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG score	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
B symptoms[9]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Tumor tissue sample[10]	X														
Electrocardiogram[11]	X		X	X	X	X	X	X	X	X	X	X	X		
Echocardiography[11]	X														
Tumor response assessment (PET-CT, CT or MRI, etc.) [12]	X				X			X			X	X		X	
Laboratory tests															

	Screening period[1]	**Treatment period**										**Follow-up period**		
Time (week)		**Week 1**	**Week 3**	**Week 5**	**Week 7**	**Week 9**	**Week 11**	**Week 13**	**Week 15**	**Week 17**	**Week n**	**Treatment termination**[2]	**Safety follow-up**[3]	**Progressive disease follow-up**[4]	**Survival follow-up**[5]
Time (Day)	**Day -28 to Day 0**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day n**	**End of treatment visit**	**Day 30 and Day 90 after the last dose**	**Once every 6 weeks/every 12 weeks**	**Once every 3 months**
Time window (day)			**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**		**± 7 days**	**± 7 days**	**± 7 days**
Blood routine, urine routine, and stood routine[13]	X		X	X	X	X	X	X	X	X	X	X	X		
Clinical chemistry[14]	X			X		X		X		X	X	X	X		
LDH and β2-MG	X			X		X		X		X	X	X	X		
Thyroid function[15]	X			X		X		X		X	X	X	X		
Pregnancy test[16]	X											X	X		
Hepatitis B surface antigen[17]	X														
Hepatitis C antibody[17]	X														
Anti-HIV antibody	X														
Treponema pallidum antibody	X														
Biomarkers[18]															
PD-L1, PD-L2 expression	X														
dMMR and/or MSI	X														
TMB	X														
Immune cell typing[19]		X		X		X		X							
Cytokine[20]		X		X		X		X							
Bone marrow aspiration/biopsy[21]	X														
Anti-GB226 antibody blood sampling[22]		X		X		X		X		X	X	X			

	Screening period[1]	Treatment period											Follow-up period		
Time (week)		**Week 1**	**Week 3**	**Week 5**	**Week 7**	**Week 9**	**Week 11**	**Week 13**	**Week 15**	**Week 17**	**Week n**	**Treatment termination[2]**	**Safety follow-up[3]**	**Progressive disease follow-up[4]**	**Survival follow-up[5]**
Time (Day)	**Day -28 to Day 0**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day n**	**End of treatment visit**	**Day 30 and Day 90 after the last dose**	**Once every 6 weeks/every 12 weeks**	**Once every 3 months**
Time window (day)			**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**		**± 7 days**	**± 7 days**	**± 7 days**
Adverse event[23]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administration of GB226		X	X	X	X	X	X	X	X	X	X				
Survival													X	X	X
Subsequent anti-tumor treatment													X	X	X

Notes:

1. During the screening period, all laboratory tests, physical examinations, weight, vital signs, electrocardiogram, echocardiography, ECOG performance status score, and pregnancy test must be completed within 7 days before the first administration of the investigational drug.
2. If a subject who has received GB226 treatment decides to discontinue the investigational drug for any reason, the subject should complete the end of treatment visit as soon as possible within 14 days after deciding to discontinue the treatment (the examination results after the last treatment within the past 14 days are acceptable).
3. Subjects who have received GB226 treatment at least once need to undergo a safety follow-up at 30 days (±7 days) after the last administration or before starting a new anti-tumor treatment (if this follow-up overlaps with the end of treatment visit, there is no need to repeat the examinations), whichever occurs first. If a new anti-tumor treatment has not been started, the subject should complete a safety follow-up again at 90 days (±7 days) after the last administration where possible.
4. Subjects who have not yet had PD after the end of treatment and have not started any subsequent anti-tumor treatment will still need to be followed up for progressive disease every 6 weeks (±7 days) in the first year from the start of investigational medication, and every 12 weeks (±7 days) in the second year and thereafter until the subject has PD, starts a subsequent anti-tumor treatment, dies or is lost to follow-up.
5. After the last safety follow-up or after the end of progressive disease follow-up (whichever occurs later), a survival follow-up will be carried out every 3 months (±7 days) (if the subject has not undergone safety follow-up, the time will be counted from the last visit) until the study ends, or the subject dies or is lost to follow-up. The follow-up can be conducted by telephone to mainly record the patient's survival and subsequent anti-tumor treatment/drugs.
6. Subjects who have been histopathologically diagnosed with PMBCL by the study site and met the inclusion criteria will be included in this study. The study site will provide the tissue specimens (stained sections, unstained slices or wax blocks, according to actual needs) of the subjects used for pathological diagnosis to the Pathology Central Laboratory for histopathological diagnosis and confirmation, and the study site should cooperate with such provision. The pathological diagnosis results of the Pathology Center Laboratory are only used for the confirmation of the enrolled population, and not used as the basis for the screening and enrollment of subjects.

7. The height is only measured during the screening period, and the weight is recorded at baseline for the calculation of the dose of the investigational drug. It will be measured every 2 weeks for dose calculation in the subsequent study process. When the change in body weight exceeds ±5% of the baseline body weight, an adverse event (AE) should be reported.
8. A comprehensive physical examination also includes a complete skin examination. Attention should be paid to areas with lymph nodes, including Waldeyer's ring, as well as liver and spleen size and nasopharyngeal examinations.
9. B symptoms include unexplained fever, body temperature > 38°C; repeated night sweats in the past month; unexplained weight decrease of 10% or more within 6 months.
10. Archived tissue specimens and/or fresh tissue specimens of the tumor need to be sent to the central laboratory for testing of biomarkers (PD-L1 and PD-L2 expression, etc.).
11. The electrocardiogram should be performed within 7 days before the first administration, 3 days before each administration, at the end of treatment visit and during safety follow-up. It can be tested at any time if necessary during treatment. Echocardiography is only performed during the screening period, and can be performed additionally in case of any cardiac discomfort or ECG abnormality during the treatment period.
12. Subjects will undergo an imaging tumor assessment every 6 weeks (±7 days) in the first year, and every 12 weeks (±7 days) in the second year and thereafter (the interval between the first efficacy evaluation and the first administration of the investigational drug must be ≥ 6 weeks, except for cases where progressive disease is considered). The International Working Group (IWG)'s response criteria for non-Hodgkin lymphomas and its amendment (2014 Lugano Classification) will be used for initial evaluation, staging and response assessment. During the screening period, the baseline imaging assessments should include both PET-CT and diagnostically valuable enhanced CT/MRI examinations of the neck, chest, abdomen and pelvis. If there are special clinical indications, a head MRI examination is also required. If any site of possible bone metastasis suggested by PET-CT is not covered by conventional examinations, CT or X-ray should be used to confirm the location of the disease, and later the disease should be followed up with the same scanning method. Imaging examinations that are routinely performed for clinical diagnosis and treatment can be used as screening examinations, provided that they meet the diagnostic quality requirements and have been performed within 28 days before the first administration. Subjects should be examined with the same imaging techniques throughout the study period. At the end of treatment visit after Week 13 and Week 19, a PET-CT examination must be additionally performed for imaging assessment; for efficacy evaluations at other time points, if the investigator judges that the addition of PET-CT examination is more conducive to the accurate evaluation of efficacy, a PET-CT examination can be performed with the consent of the sponsor. The time for imaging examinations should follow the calendar day, and should not be adjusted according to the delay in the start of the cycle or the extension of the treatment cycle. After evidence of progression (if the subject is clinically stable) or response that meets the definition of Lugano criteria, repeat examinations are required at the next evaluation time point to confirm the efficacy.
13. Blood routine, urine routine, and stood routine should be completed within 7 days before the first administration, at the end of treatment visit and during safety follow-up. Blood routine and urine routine should be performed within 3 days before the administration every 2 weeks. The stood routine is not mandatorily required during the treatment period, and can be tested at any time if necessary.
14. Blood biochemistry (including fasting blood glucose), lactate dehydrogenase (LDH) and β2 microglobulin tests should be completed within 7 days before the first administration, within 3 days before administration every 4 weeks, at the end of treatment visit and during safety follow-up.
15. Thyroid function includes free thyroxine (FT3/FT4) and thyroid-stimulating hormone (TSH) tests, which are performed within 7 days before the first administration, within 3 days before administration every 4 weeks, at the end of treatment visit and during safety follow-up.
16. Pregnancy test: Women of childbearing age who are not postmenopausal or have not undergone surgical sterilization should take a serum β-human chorionic gonadotropin (β-hCG) pregnancy test within 7 days before the first administration, at the end of treatment visit, and during safety follow-up. During the treatment period, the investigator will determine whether a serum pregnancy test is necessary.
17. If HBsAg is positive, HBV-DNA quantitation needs to be additionally tested; if HCV-Ab is positive, HCV-RNA quantification needs to be additionally tested; only subjects with HBV-DNA or HCV-RNA quantitation less than the upper limit of normal of the detection unit can be enrolled.
18. Biomarker testing includes programmed cell death protein ligand-1 (PD-L1), programmed cell death protein ligand-2 (PD-L2), deficient mismatch repair genes (dMMR) and/or microsatellite instability (MSI) and tumor mutation burden (TMB). For the collection, processing, storage and transportation of tumor tissue samples and blood samples of biomarkers, please refer to the corresponding Central Laboratory Manual. If the subject's tissue samples are insufficient, the collection of tissue samples for PD-L1 and PD-L2 testing should be guaranteed.

19. Immune cell typing includes B lymphocytes [CD19+], T lymphocytes [CD3+] and their subtypes [CD4+ and CD8+ T cells] and NK cells [CD16+CD56+], which should be tested in the study site's laboratory within 7 days before the first administration, and before administration at Weeks 5, 9, and 13 (± 3 days). If the study site is incapable of such testing, fresh anticoagulated whole blood must be sent to the central laboratory for testing within 24 hours.
20. Cytokine testing includes interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor α (TNFα) and interferon γ (INFγ), respectively, which should be tested in the study site's laboratory within 7 days before the first administration, and before administration at Weeks 5, 9, and 13 (± 3 days). If the study site is incapable of such testing, serum must be sent to the central laboratory for testing.
21. During the screening period, combined with the subject's clinical symptoms and the results of laboratory tests and PET-CT examinations, the investigator will decide whether to complete a bone marrow aspiration/biopsy. The examination results of diagnostic quality within 2 weeks before the signing of the ICF are acceptable. Patients with positive bone marrow examinations during the screening period need to be re-examined when the subsequent efficacy evaluation is CR or when a bone marrow lesion is suspected to be new or recurring. During the treatment period, the investigator can decide whether to perform bone marrow aspiration/biopsy and its frequency according to the diagnosis and treatment routines.
22. Anti-drug antibody (ADA) blood sample collection time points: Blood samples should be collected from subjects within 1 hour before the first administration, within 24 hours before administration every 4 weeks, and at the end of treatment visit, and sent to the central laboratory for testing and analysis.
23. From the signing of the ICF to 90 days after the last study administration of GB226, all AEs and SAEs will be collected; after 90 days following the last study administration of GB226, only investigational drug-related AEs and SAEs will be collected.

ABBREVIATIONS AND TERMINOLOGY

Abbreviation	Full name in English
ADA	Anti-drug antibody
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspertate Aminotransferase
B-NHL	B cell non-Hodgkin lymphoma
CR	Complete response
CRF	Case Report Form
d，D	day
DLBCL	Diffuse Large B Cell Lymphoma
DOR	Duration of response
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practice
h	hour
HL	Hodgkin Lymphoma
HLA	Human Leucocyte Antigen
IEC	Independent Ethic Committee
IPI	International Prognostic Index
IRB	Institution Review Board
IRC	Independent Review Committee
irAEs	immune-related adverse events
kg	Kilogram
L	liter
LDH	Lactate Dehydrogenase
MMR	Mismatch Repair
mg	milligram
MHC	Major Histocompatibility Complex
min	minute
ml，mL	milliliter
MSI	Microsatellite Instability
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin Lymphoma
NOAEL	no-observed-adverse-effect-level
NMPA	National Medical Products Administration
NSCLC	Non-small cell lung cancer
OS	Overall survival
ORR	Overall Response Rate
PMBCL	Primary mediastinal large B cell lymphoma
PD-1	Programmed cell death protein-1
PFS	Progression free survival

Abbreviation	Full name in English
PD	Disease progression
PR	Partial response
PS	Performance Scoring
RT	Radiation Treatment
SAE	Severe Adverse Event
SAP	Satistical Analysis Plan
TCR	T cell receptor
TILs	Tumor-infiltrating lymphocytes
TMB	Tumor Mutation Burden
TTR	Time to Response
ULN	Upper Limit of Normal

1 INTRODUCTION

1.1 Study Background

1.1.1 Primary mediastinal large B cell lymphoma (PMBCL)

PMBCL is a rare pathological subtype of lymphomas, belonging to diffuse large B-cell lymphomas (DLBCL), and accounting for 6-13% of all DLBCL and 2-4% of all NHL. It mostly occurs in young women, and often clinically manifests as a large mediastinal mass, often invading the pleura and pericardium, causing pleural effusion or pericardial effusion, and usually accompanied by superior vena cava syndrome. Eighty percent of patients are at Stage I-II when newly diagnosed, and only 20% of patients are at Stage III-IV when newly diagnosed. The disease usually involves the kidneys and adrenal glands[1].

The overall prognosis of PMBCL is good. About 90% of patients can be cured. The International Prognostic Index (IPI) score is currently the most important prognostic factor. A study by the BCCA in Canada showed that LDH increased to 2 times the upper limit of normal, age above 40 years, and PS score of 2 points or more would suggest a poor prognosis. The International Extranodal Lymphoma Study Group (IELSG) has pointed out that male, poor PS, and advanced disease are associated with poor prognosis. Among 181 Japanese patients receiving RCHOP±RT treatment (selected from the extensive population receiving a wide range of therapies), high IPI and serous effusion were their poor prognostic factors. An abstract in Vancouver in 2012 suggested that among 96 patients receiving RCHOP±RT treatment, serous effusion, B symptoms, and age were their poor prognostic factors[2].

The first-line treatment of PMBCL is mainly rituximab combined with chemotherapy. Radiotherapy and autologous peripheral stem cell transplantation are still controversial. The ESMO guidelines recommend that rituximab combined with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or combined with V/MACOP-B (methotrexate, daunorubicin, cyclophosphamide, vincristine, prednisone and bleomycin) or R-CHOP14 or dose-adjusted R-DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) for stronger combination chemotherapy can be used as the preferred treatment for PMBCL. The first-line treatment regimen recommended by the 2017 NCCN guidelines includes: 6 courses of R-DA-EPOCH with optional add-on radiotherapy for persistent local disease; 6 courses of RCHOP+ mediastinal radiotherapy, and 4 courses of RCHOP + sequential 3 courses of ICE+/-radiotherapy (Category 2B)[3]. More and more trials have confirmed that in PMBCL patients treated with the R-DA-EPOCH regimen, radiotherapy did not significantly improve the PFS and OS of patients. At present, there is still controversy over whether radiotherapy should be performed after immunochemotherapy. A randomized, open-label, double-arm Phase III clinical trial (Clinical trial ID: NCT01599559) is in progress. The significance of high-dose chemotherapy combined with autologous peripheral stem cell transplantation (ASCT) for the initial treatment of high-risk PMBCL patients is still unclear. Most reports are sample-size retrospective analyses. The OS is similar to that of conventional chemotherapy. Hence, such combination therapy is not recommended as a first-line treatment regimen. However, it is an option for relapsed and

refractory PMBCL. For relapsed and refractory PMBCL that has progressed after or been resistant to first-line treatment, traditional palliative treatment has poor efficacy and extremely poor prognosis (the ORR is 0-25%, and the 2-year OS rate is 15%)[7]. A recent phase II trial of Brentuximab vedotin monotherapy has been early terminated due to the extremely low ORR during the interim analysis (2/15, 13%).

Studies have shown that PMBCL has significantly different gene expression profile, clinical and biological characteristics from other types of DLCBL, but it is very similar to Hodgkin lymphoma (cHL), especially nodular sclerosing HL arising from the mediastinum. Different lymphoma subtypes have their special microenvironment composition, and there is cross signal transduction between tumor cells and other immune cells in the microenvironment. PMBCL has a highly heterogeneous tumor microenvironment and is very similar to cHL (diverse other immune cell types, relatively few tumor cells). On the contrary, DLBCL has a tumor microenvironment with a large number of highly homogeneous tumor cell components, suggesting the mechanism of inflammatory cell infiltration in the tumor microenvironment of PMBCL[10]. In addition, studies have found that 70% of PMBCL has amplification or translocation of 9p24.1 chromosome, which includes CD274 (encoding PD-L1), PDCD1LG2 (encoding PD-L2) and other alleles. This chromosome has a mutation rate of 30% in HL, but is very rare in other types of B-cell lymphomas such as DLBCL. As a result, high expression of PD-L1 and PD-L2 proteins is very common in PMBCL, but rare in DLBCL. And PD-L1 in most PMBCL is highly expressed in tumor-associated macrophages (TAM). A study found that the expression of PD-L2 in PMBCL was higher than that of PD-L1, and the protein expression of PD-L2 detected in the tissue microarray was 5.6 times higher than that in DLBCL[10].

In addition, studies have found that in cHL and PMBCL, mutations in the major histocompatibility complex (MHC) class II trans-activator (CIITA) of transcription gene located on chromosome 6p13.13 can cause inactivation of the expression of human leukocyte antigen (HLA) MHC class II transcription factor. Chromosomal translocation can lead to the fusion of CIITA and CD274 or PDCD1LG2 loci, resulting in high expression of PDL protein. Therefore, these two tumor subtypes are likely to use the PD-1 pathway and HLA expression variation to form a mechanism to achieve immune superiority, thereby allowing immune escape[12].

Studies have shown that 70% of cHL, 54% of predominantly nodular sclerosing HL, and 35% of PMBCL have more than 5% of tumor cells expressing PD-L1. Relapsed or refractory HL has a significant increase in PD-1 positive tumor infiltrating T cells. Coupled with 9p24.1 chromosome mutations and high expression of PD-L1, the ORR of PD-1 inhibitor monotherapy can reach 65%-87%, with a median duration of response up to 16 months. The efficacy of PD-1 inhibitors in PMBCL has also been verified recently. A phase Ib clinical trial KEYNOTE-013 confirmed that pembrolizumab (Keytruda) had demonstrated good efficacy in relapsed or refractory PMBCL. Among 17 patients, the ORR was 41%, the CR rate was 12%, and the other 6 patients had SD (35%)[14].

KEYNOTE-170 (NCT02576990) was a multi-center, open-label, single-arm phase II clinical trial including a total of 53 patients with relapsed or refractory PMBCL. The median age was

33 years (20-61 years), 57% were women, and 92% were white. The patients received a median of 3 lines (2-8 lines) of treatment before enrollment, 36% of the patients had primary drug resistance, 49% of the patients were resistant to the last treatment after the disease relapsed, and 15% had not been treated yet after the relapse. Twenty-six percent of the patients had undergone autologous hematopoietic stem cell transplantation (HSCT), 32% had received radiotherapy, and all patients had received rituximab therapy previously. The median follow-up time was 3.5 months (1 day to 22.8 months). Among the 24 effective cases, the ORR was 45%, of which the CR rate was 11%, the PR rate was 34%, and the median time to objective response was 2.8 months. The treatment was stopped due to adverse reactions in 8 subjects and interrupted due to adverse reactions in 15 subjects. Twenty-five percent of subjects experienced adverse reactions requiring systemic corticosteroid therapy. Twenty-six percent of subjects experienced SAEs, including arrhythmia (4%), pericardial tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Other clinically important adverse reactions with an incidence of less than 10% included hypothyroidism (8%), hyperthyroidism and pericarditis (4% each), thyroiditis, pericardial effusion, pneumonia, arthritis and acute renal failure (2% each). There was good safety overall. Therefore, the US FDA quickly approved Keytruda on June 13, 2018 for the indication of "adults and children with refractory or relapsed PMBCL after second-line and above treatment" based on this study[15].

1.1.2 Overview of programmed cell death receptor-1 (PD-1)

1.1.2.1 Mechanism of action of PD-1 pathway

PD-1 (CD279) is a co-inhibitory receptor expressed on the surface of T cells, B cells, monocytes, and natural killer cells. It is encoded by the PDCD1 gene located at 2q37.3 and is a 55 kDa transmembrane protein. The expression of PD-1 is up-regulated on the surface of immune cells involved in antigen recognition, which is one of the signs of immune cell activation. PD-1 acts as an inhibitory receptor, and its downstream signals inhibit the proliferation of T cells and the release and killing effect of cytokines. In tumor models, PD1 binds to the PD-L1 of tumor cells to inhibit T cells and block the tumor immune response. In vitro tests have shown that inhibiting the interaction between PD-1 and PD-L1 can enhance T cell response and mediate anti-tumor activity.

PD-1 has two main ligands: PD-L1 and PD-L2. The PD-L1- and PD-L2-encoding genes in human cells are both at 9q24.2. PD-L1 and PD-L2 have similar encoding genes and structures, but their characteristics are different. For example, PD-L1 is widely expressed on T cells, B cells, monocytes, macrophages, dendritic cells, a variety of tumor cells and some non-lymphatic tissue, while PD-L2 is only expressed on activated macrophages, dendritic cells and some tumor cells; PD-L1 is the main ligand of PD-1, but PD-L2 has a affinity for PD-1 2-6 times higher than PD-L1; PD-L1 is mainly induced by IFN-γ, while PD-L2 is more sensitive to IL-4.

T cell activation mainly depends on the costimulatory signal generated by CD3/CD28 activation: after binding to the ligand, CD28 ligand-dependent tyrosine phosphorylase can promote the aggregation and activation of phosphatidylinositol 3-kinase (PI3K), resulting in an increase

in intracellular 3-phosphorylated lipids. These lipids can activate protein kinase B (Akt), and promote cytokine synthesis, glucose transporter expression, glycolysis and cell survival. With the participation of PD-1 ligands, PD-1 binds to the SH-2 domains contained in SHP-1 and SHP-2 to inhibit early T cell receptor (TCR) signal transduction through dephosphorylation of Akt kinase, PI3K, ZAP-70, PKC-θ and CD3δ molecules. The other ligand of PD-L1 is B7-1 (CD80). The specific binding of PD-L1 and B7-1 (CD80) can block the CD28:B7 costimulatory signal, thereby inhibiting T cell activation. In addition, tests have confirmed that after the activation of the PD-1/PD-L1 pathway, it is highly likely to down-regulate the activity of the Akt pathway to induce the production of regulatory T cells and maintain their functions, thereby exerting an immunosuppressive effect. Unlike PD-L1, PD-L2 cannot bind to B7-1, but can bind to repulsive guidance molecule b (RGMb) without the involvement of PD-1, and is involved in maintaining the immune tolerance state of the respiratory system.

1.1.2.2 PD-1 participation in tumor immunity

There are two hypotheses about the main mechanism of PD-1 participating in tumor immune escape: a. inherent mechanism: the genome or transcriptome mutations of tumor cells lead to high expression of PD-L1. The most common is the abnormal activation of the tumor's inherent Akt, STAT3 and other signaling pathways and induction of high PD-L1 expression, thereby inhibiting the activation of cytotoxic T cells. For example, the deletion of PTEN gene in many tumors usually leads to excessive activation of the PIK3/Akt signaling pathway, thereby causing an increase in the downstream PD-L1 expression; in primary mediastinal large B-cell lymphomas and nodular sclerosing Hodgkin lymphomas, the increased 9p24.1 copy number results in high expression of PD-L1 and PD-L2 located at 9p24. In addition, 9p24 amplification can activate JAK2/STAT, which can promote tumor growth while promoting PD-1 ligand expression. b. Adaptive mechanism: A protective mechanism of tumor cells against the clearance of immune cells in the immune microenvironment. Tumor cells highly express PD-L1 under the induction of IFN-γ secreted by a series of cells involved in tumor clearance (CD4+ Th1 cells, activated T cells, activated natural killer cells). In addition, IFN-γ can also increase the immunosuppressive IDO content in TME and promote tumor PD-L1 expression. Apart from the surface of tumor cells, the expression of PD-L1 can also be detected in TILs in TME. Studies have shown that the expression of PD-L1 in TILs can better predict the efficacy of anti-PD-1 treatment compared with the expression of PD-L1 in tumor cells.

PD-1 is not only involved in the regulation of tumor immunity, but also plays a certain role in the process of tumor occurrence, growth and metastasis. PD-L1 is expressed in situ on many solid tumor tissues, including breast cancer, lung cancer, ovarian cancer, melanoma, bladder cancer, liver cancer, gastric cancer and head and neck cancer. Its expression level is strongly correlated with the poor prognosis of the tumor. The high expression of PD-L1 in cancer cells can not only induce tumor-specific T lymphocyte dysfunction and apoptosis, but also enhance TIL secretion of immunosuppressive inflammatory cytokines, and promote the proliferation, anti-apoptosis and metastasis of cancer cells.

1.1.2.3 PD-1 product introduction

Programmed death-1 (PD-1) and its ligand (PD-L1) inhibitors are immune checkpoint monoclonal antibodies, which have become a hot spot in tumor immunotherapy research in recent years. The PD-1 inhibitors that have been approved for marketing by the FDA include nivolumab and pembrolizumab, and PD-L1 inhibitors include atezolizumab, durvalumab and avelumab. PD-1 has currently been approved by the FDA for the following indications: melanoma and non-small cell lung cancer, renal cell carcinoma, classic Hodgkin lymphoma, head and neck squamous cell carcinoma, bladder cancer, urothelial cancer, colorectal cancer, hepatocellular carcinoma, gastric cancer and microsatellite instability-high cancer.

The results of Trial KEYNOTE-013 showed that the ORR of pembrolizumab in the treatment of relapsed and refractory mediastinal large B-cell lymphoma (PMBCL) was 41%, the CR was 12%, and the other 6 patients had SD (35%)[14]. The results of the phase II clinical trial KEYNOTE-170 (NCT02576990) showed that a total of 53 subjects were enrolled, and their ORR was 45%, of which the CR rate was 11%, and the PR rate was 34%. The overall safety profile was good. Therefore, the US FDA has recently approved Keytruda for the treatment of relapsed and refractory PMBCL based on this study[15].

Both nivolumab and pembrolizumab have good safety and tolerability. Common adverse reactions (>2%) included immune-mediated pneumonia, colitis, hepatitis, nephritis, renal insufficiency, and hypothyroidism or hyperthyroidism. Studies have shown that most adverse reactions were grade 1-2[16].

1.2 Introduction to GB226

GB226, recombinant humanized anti-PD-1 monoclonal antibody (code GB226) jointly developed by Genor Biopharma Co. Ltd. and Crown Bioscience, is an IgG4κ type monoclonal antibody expressed in the Chinese hamster ovary (CHO) cell expression system by using deoxyribonucleic acid (DNA) recombination technology. GB226 has a completely new amino acid sequence and molecular structure different from the two marketed anti-PD-1 monoclonal antibodies.

Drug name

Generic name: Genolimzumab Injection

Trade name: None

English name: Genolimzumab Injection

Investigational drug code: GB226

Basic physicochemical properties

Ingredient: Recombinant humanized anti-PD-1 monoclonal antibody.

Molecular weight: 144 kDa.

Preparation: Colorless to light yellow liquid, 70 mg/7 ml/vial.

Pharmacological mechanism

By binding to the PD-1 receptor, GB226 blocks the interaction between PD-1 and its ligand PD-L1/PD-L2, and relieves the immunosuppressive effect mediated by the PD-1 pathway, including the anti-tumor immune response.

Pre-clinical trial

Pharmaceutical tests have shown that the GB226 cell line is of safe source, stable production technology, controllable quality, stable preparation, and good compatibility with packaging materials, and meets the conditions for industrialization. It thus can provide safe, effective and quality-controllable products for clinical trials. Pharmacodynamic tests have shown that GB226 has a clear target, a clear mechanism of action, and a significant tumor suppression effect. Toxicological tests have shown that the toxicity of this product is low and reversible at high doses, and the most common toxicity is unique to the drug's mechanism of action.

1.2.1 Clinical trials conducted

After obtaining the clinical trial approval letter in China (2016L10520), Genor Biopharma Co. Ltd. first carried out the single and repeat-dose escalation clinical trials of GB226 (Gxplore-001) according to the guidance requirements of the CFDA, and entrusted the Cancer Hospital, Chinese Academy of Medical Sciences, Harbin Medical University Cancer Hospital and other study sites to evaluate the safety, tolerability and pharmacokinetic characteristics of GB226 in patients with target tumor types, explore the optimum biologically effective dose, and to observe the preliminary anti-tumor activity of GB226 so as to provide a basis for further exploratory clinical studies. The partner CB Therapeutics Inc. carried out a phase I clinical trial (CBT-501-01) of this product in Australia at the same time.

Gxplore-001 screened and enrolled histologically or cytologically diagnosed patients with advanced (stage IIIb, stage IIIc, unsuitable for multidisciplinary treatments), metastatic (stage IV) or relapsed solid tumors [including melanoma, NSCLC, renal cancer, head and neck cancer, esophageal cancer, liver cancer, bladder cancer, glioblastoma (2016 version of WHO, grade IV, excluding brain stem and cerebrospinal fluid disseminated glioblastoma)] or lymphoma (classic Hodgkin lymphoma and/or peripheral T-cell lymphoma, NK-T-cell lymphoma, primary mediastinal large B-cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma and other non-Hodgkin lymphomas) who were inoperable, had failed or could not tolerate systemic treatment, and/or had no effective standard treatment available. The study consisted of 2 parts (single-dose and multiple-dose). Dose escalation exploration was adopted, and each part involved 3 dose groups, namely 1 mg/kg, 3 mg/kg, and 10 mg/kg. The study was divided into a main study phase and a continued treatment phase. Main study phase: in the single-dose group, the subjects were followed up to Week 8 after a single dose; in the multiple-dose group, the subjects were administered every 2 weeks for a total of 6 times, and followed up to Week 12. Subjects who had completed the main study could enter the continued treatment phase at the discretion of the investigator. The single-dose group was given the original dose every 3 weeks, and the multiple-dose group was given the original dose every 2 weeks until progressive disease or intolerance. The treatment could continue for up to 2 years.

As of August 31, 2018, the median follow-up time after the first administration was 95.5 days (range: 16-290 days), and a total of 42 subjects were enrolled, including 15 single-dose subjects and 27 multiple-dose subjects. The completion of the study by subjects in each dose group is shown in Table 2. The median age of the subjects was 53 years old (range: 21-65 years); there were 28 males and 14 females; the ECOG score was 0 points in 18 (42.9%) subjects and 1 point in 23 (54.8%) subjects; the KPS score was 60 points in 1 subject. The median weight was 65.5 kg (range: 46.0-90.0 kg), and the median BMI was 23.13 kg/m^2 (range: 17.5-31.2 kg/m^2).

The tumor types of subjects enrolled included 13 cases of non-Hodgkin lymphoma, 6 cases of Hodgkin lymphoma, 6 cases of head and neck cancer, 8 cases of lung cancer (4 cases of adenocarcinoma, 4 cases of squamous cell carcinoma), 4 cases of melanoma, 2 cases of esophagus cancer, 1 case of glioblastoma, 1 case of renal clear cell carcinoma, and 1 case of mediastinal small cell carcinoma.

During the 28-day DLT observation period, no DLT event was observed in all dose groups, and the MTD was not reached. During the treatment period, 39 (92.9%) subjects experienced treatment-emergent adverse events (TEAE), including 16 (38.1%) subjects who experienced CTCAE grade 3 and above TEAEs. A total of 33 (78.6%) subjects experienced treatment-related adverse events (TRAE). TRAEs with an incidence of ≥10% included alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hyperthyroidism, blood thyroid-stimulating hormone increased, free thyroxine increased, platelet count decreased, lymphocyte count decreased, and fever. A total of 6 (14.3%) subjects experienced grade 3 TRAEs, including γ-glutamyltransferase increased, aspartate aminotransferase increased, white blood cell count decreased, lymphocyte count decreased, hemoglobin decreased, platelet count decreased, and neutrophil count decreased. See Table 3 for details. No grade 4-5 TRAEs occurred. During the treatment, a total of 8 (19%) subjects experienced immune-related adverse events (irAE), all grade 1-2, including liver injury, hypothyroidism, hyperthyroidism, thyroiditis, blood thyroid stimulating hormone increased, free thyroxine increased, free thyroxine decreased, and interstitial lung disease. A total of 11 subjects experienced SAEs, of which 2 SAEs were possibly related to treatment, namely atrial fibrillation and liver injury. There were 8 deaths, of which 7 were judged to be unrelated to the study drug, and the correlation of the remaining 1 death was indeterminable for the time being.

As of August 31, 2018, 35 subjects had undergone tumor response evaluation. Among them, the best response observed was PR in 9 (25.7%) subjects and SD in 15 (42.9%) subjects, suggesting that GB226 had certain efficacy.

The pharmacokinetic results showed that after a single administration of GB226, within the range of 1-10 mg/kg, its AUC and Cmax increased in a dose-dependent manner, and exhibited linear pharmacokinetic characteristics; the half-life was prolonged with the increase of the dose, and the time to peak was prolonged with the increase of the administered dose. After multiple administrations of GB226 q2w (q2w×6), subjects already reached a steady state before the sixth administration. As shown in Figure 1, the exposure of GB226 increased with the increase in the dose, and the time to peak was basically unchanged with the increase in the administered

dose. The half-life in each dose group was correspondingly longer than that of a single administration. The geometric mean values of the accumulation factor AR_{AUC} in the 3 mg/kg and 10 mg/kg dose groups were 2.8578 and 2.1382, respectively, suggesting that GB226 had a certain degree of accumulation after intravenous infusion once every 2 weeks. The pharmacokinetic curves of GB226 after single and multiple administrations are shown in Figure 2 and Figure 3, respectively.

The pharmacodynamic study showed that after GB226 administration, the PD-1 receptor occupancy on CD8+ T cells in each dose group (1, 3, and 10 mg/kg) increased rapidly, and continued to be maintained above a level of 80%. After a single administration, the receptor occupancy could be maintained above a level of 80% for 56 days. After multiple administrations, the receptor occupancy could be stably maintained at a level of 80%.

The results of the immunogenicity study showed that among the 42 subjects, a total of 4 (9.5%) subjects were ADA positive at least once after medication, including 2 in the 1 mg/kg single-dose group, 1 in the 3 mg/kg single-dose group, and 1 in the 1 mg/kg multiple-dose group. The subjects in the other dose groups were not positive for ADA.

The CBT-501-01 study carried out in Australia was an open-label, dose escalation phase I study. The subject population was patients with relapsed advanced or metastatic solid tumors, who were divided into 3 dose groups (1, 3, and 10 mg/kg) to receive repeated administrations (q2w) until progressive disease or intolerance to explore the safety, tolerability, pharmacokinetics, immunogenicity and preliminary efficacy of dose escalation. The study enrolled the first subject in March 2017, and the dose escalation phase of 1, 3, and 10 mg/kg has been completed. So far, enrollment of 3 subjects each in the 1 mg/kg and 3 mg/kg dose groups, 6 subjects in the 10 mg/kg dose group, and 6 subjects in the expansion 3 mg/kg dose group has been completed. As of September 30, 2018, a total of 18 subjects were enrolled. All subjects had no DLT events observed during the 28-day DLT observation period, did not reach the MTD, and showed good overall tolerability. Treatment-related adverse events (TRAE) with an incidence of ≥10% included hyperthyroidism, diarrhea, fatigue, and dry mouth; a total of 2 (11.1%) subjects experienced grade 3 TRAEs, including diarrhea, serum alkaline phosphatase increased and γ-glutamyltransferase increased; irAEs occurred in 7 subjects, including hyperthyroidism and hypothyroidism, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, liver injury, pruritus, and macula.

The phase I dose-escalation study of Genolimzumab in China and Australia showed that the 3 mg/kg dose group had good safety and tolerability, sufficient drug exposure in blood, a moderate elimination half-life, and pharmacokinetic characteristics similar to those of nivolumab 3 mg/kg. The receptor occupancy was in a saturated state, and preliminary efficacy was observed. Therefore, 3 mg/kg was recommended as the dose for the phase II study.

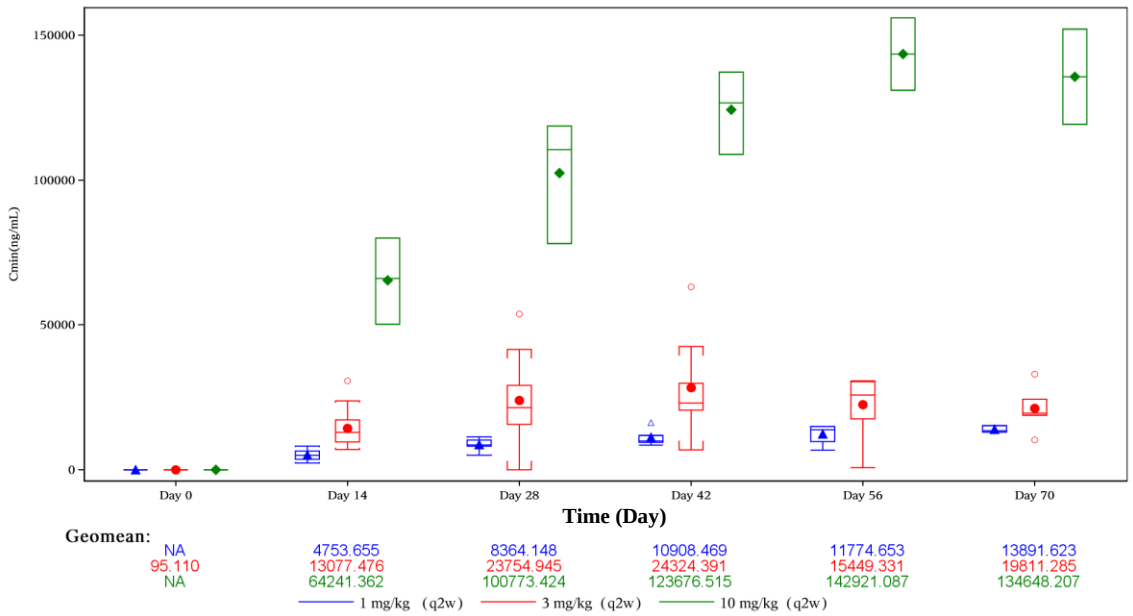

Figure 1 Steady-state evaluation of trough concentration in different dose groups (Q2W) in the multiple-dose phase (PKCS)

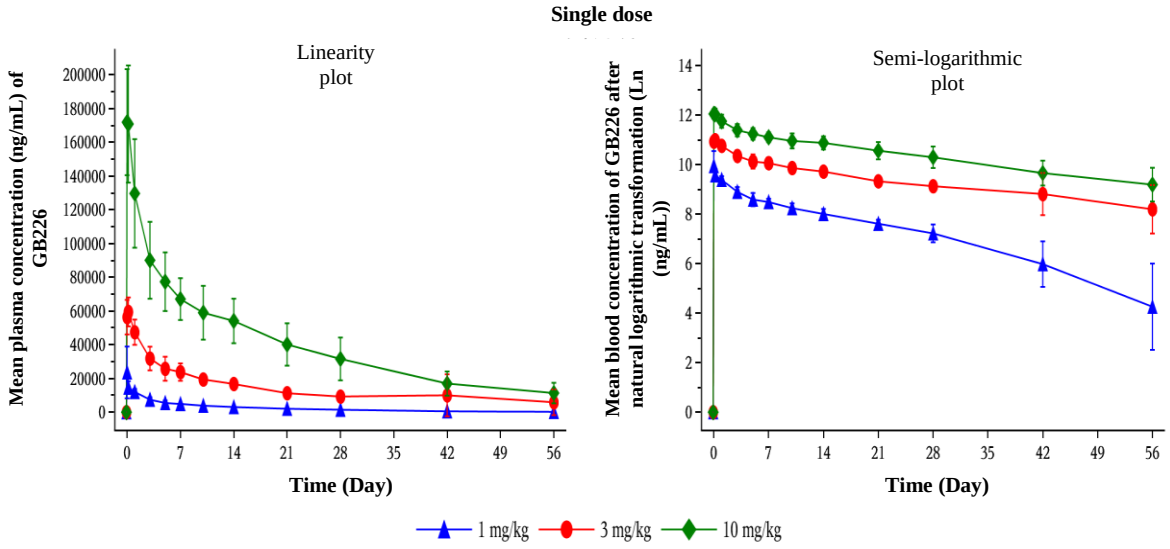

Figure 2 GB226 mean (Mean ± SD) plasma concentration-time curve (linear and semi-log)-single-dose (PKCS)

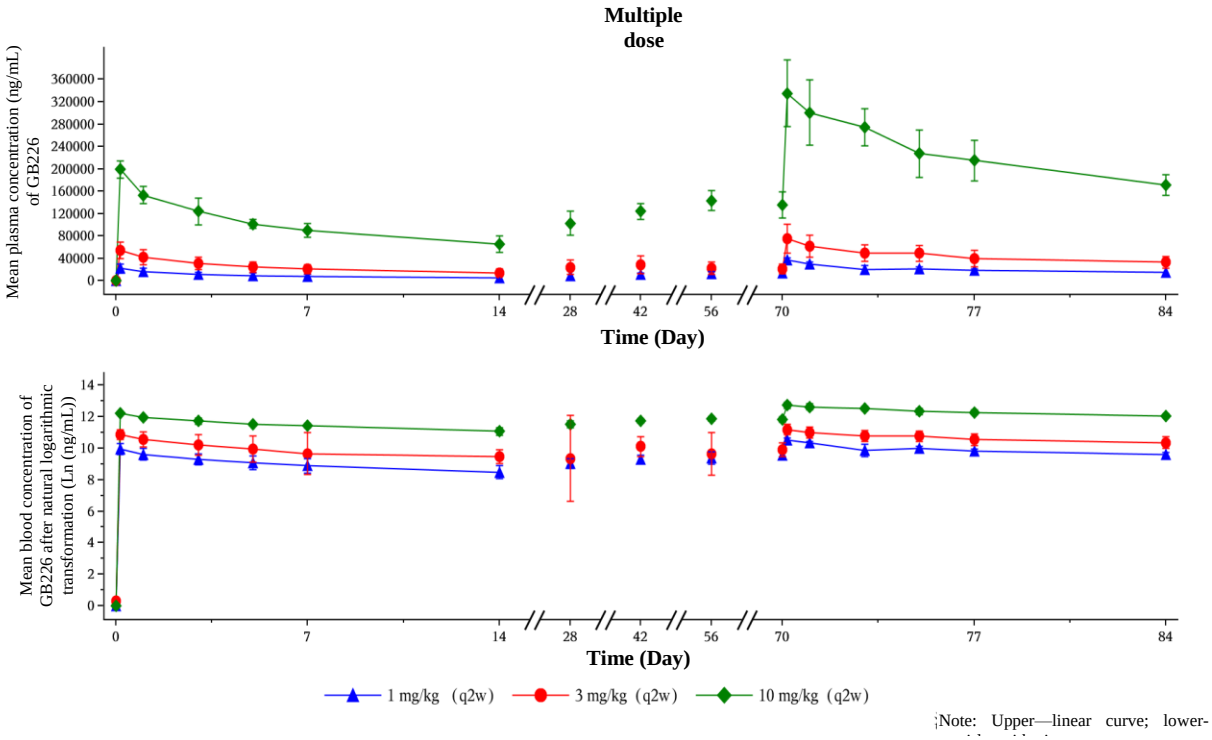

Figure 3 GB226 mean (Mean±SD) plasma concentration-time curve (linear and semi-log)-multiple-dose (PKCS)

1.3 Risks and Benefits

The population to be selected for this trial is patients with refractory or relapsed PMBCL. For patients with relapsed or refractory PMBCL after autologous stem cell transplantation or who have failed at least second-line or above systemic treatment, due to the poor efficacy of traditional palliative treatment regimens and extremely poor prognosis (the ORR is 0-25%, and the 2-year OS rate is 15%), there is currently no standard treatment regimen available, and thus participating in clinical trials is a better option for them. The NCCN guidelines recommend participating in clinical trials as one of the options for treating patients with relapsed and refractory PMBCL[3].

KEYNOTE-170 (NCT02576990) was a multi-center, open-label, single-arm phase II clinical trial including a total of 53 patients with relapsed or refractory PMBCL. The median follow-up time was 3.5 months (1 day-22.8 months). Among the 24 effective cases, the ORR of Keytruda monotherapy was 45%, of which the CR rate was 11%, the PR rate was 34%, and the median time to objective response was 2.8 months. Eight subjects stopped treatment due to adverse reactions, and 26% of subjects experienced SAEs, including arrhythmia (4%), pericardial tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Other clinically important adverse reactions with an incidence of less than 10% included hypothyroidism (8%), hyperthyroidism and pericarditis (4% each), thyroiditis, pericardial effusion, pneumonia, arthritis and acute renal failure (2% each). There was good safety overall. Therefore, based on this study, the US FDA quickly approved Keytruda for the indication of

"adults and children with refractory or relapsed PMBCL after second-line and above treatment" on June 13, 2018[15].

The investigational drug GB226 is an anti-PD-1 monoclonal antibody molecule, which has the same mechanism of action as nivolumab and pembrolizumab. The pharmacology test has demonstrated the in vitro and in vivo pharmacodynamics, mechanism of action, pharmacokinetic characteristics, and anti-tumor activity of GB226. Therefore, the benefits of patients participating in the trial can be expected.

The domestic phase I clinical study (Gxplore-001) enrolled the first subject in October 2017. As of August 31, 2018, a total of 42 cases had been enrolled, and the dose escalation studies with the single dose and multiple dose had been completed. No DLT event was observed in all dose groups (1, 3, and 10 mg/kg), and the MTD dose was not reached. Eight (19%) subjects experienced immune-related adverse events (irAE), all grade 1-2. The AEs found during the entire study period were basically the same as with Opdivo and Keytruda. The phase I clinical study of GB226 in Australia also showed that in the range of 1 mg/kg-10mg/kg, GB226 was well tolerated and safe in solid tumor patients. Most of the immune-related adverse events (irAEs) were grades 1 and 2, and the symptoms could be improved by conservative symptomatic treatment and glucocorticoid treatment. As of September 30, 2018, no DLT events had been observed, and the overall tolerability was good.

This trial protocol describes the emergency treatment plan, stipulates the criteria for subjects to terminate the trial in advance, and avoids various risks as much as possible from the design of the trial. During the implementation of the clinical trial, clinical monitors will regularly check trial data, assist investigators in reporting and handling adverse events, and report safety hazards to the sponsor; medical monitors will review safety data in a timely manner, and identify potential safety risks early, communicate with investigators and the sponsor in a timely manner, and adjust the trial protocol if necessary.

In summary, in view of the clinical needs of patients with relapsed or refractory PMBCL, based on the previous preclinical and clinical trial data of GB226 and the trial data of similar products, the benefits outweigh the risks. In the implementation of the trial, all parties will perform their duties, strictly implement the risk management plan, and minimize the risks so as to ensure greater benefits for the subjects.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the overall response rate (ORR) of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma.

2.2 Secondary Objectives

- To evaluate the duration of response (DOR) of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma;
- To evaluate the time to response (TTR) of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma;
- To evaluate the disease control rate (DCR) of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma;
- To evaluate the progression-free survival (PFS) and overall survival (OS) of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma;
- To evaluate the safety of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma;
- To evaluate the immunogenicity of GB226.

2.3 Exploratory objective

- To explore the correlation between programmed cell death protein ligand-1 (PD-L1), programmed cell death protein ligand-2 (PD-L2), and biomarkers such as deficient mismatch repair genes (dMMR) and/or microsatellite instability (MSI) and tumor mutation burden (TMB) in the tumor tissues of patients with relapsed or refractory primary mediastinal large B-cell lymphoma and the clinical efficacy of GB226
- To explore the correlation between immune cell typing and counting (B lymphocytes [CD19+], T lymphocytes [CD3+] and its subtypes [CD4+ and CD8+ T cells], NK/T cells [CD16+ and CD56+]) and cytokines (IL-2, IL-6, IL-8, TNFα and INFγ) and efficacy of GB226.

3 STUDY DESIGN

3.1 Study Design

This is a multi-center, prospective, open-label, single-arm phase II clinical trial to evaluate the efficacy and safety of GB226 in the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma, and to assess the immunogenicity of GB226. The trial plans to enroll 53 patients with relapsed or refractory PMBCL in 40 study sites in China. The trial includes 3 periods: a screening period, a treatment period and a follow-up period. Subjects must sign an informed consent form before undergoing study-related examinations and assessments. The screening period is 28 days. During the screening period, subjects will complete the assessment in accordance with the schedule of activities (Table 1), and only subjects who fully meet the enrollment conditions can be enrolled and receive treatment with GB226.

The eligible subjects will receive GB226 treatment at a dose of 3 mg/kg/time by intravenous infusion, once every two weeks, until confirmed progressive disease, intolerable toxicity, withdrawal of informed consent, start of other anti-tumor treatment, loss to follow-up or death, treatment discontinuation at the discretion of the investigator or subject, or end of the trial.

Each subject will be treated with GB226 every 2 weeks (±3 days) during the treatment period; a tumor efficacy assessment visit will be conducted every 6 weeks (±7 days) in the first year, and every 12 weeks (±7 days) in the second year and thereafter (the interval between the first efficacy evaluation and the first administration of the investigational drug must be ≥6 weeks, except for circumstances where progressive disease is considered). If a subject who has received GB226 treatment at least once decides to discontinue the investigational drug for any reason, the subject should complete the end of treatment visit as soon as possible within 14 days after deciding to discontinue the treatment (the examination results after the last treatment within the past 14 days are acceptable). Subjects who have received GB226 treatment at least once need to undergo a safety follow-up at 30 days (±7 days) after the last administration or before starting a new anti-tumor treatment (if this follow-up overlaps with the end of treatment visit, there is no need to repeat the examinations), whichever occurs first. If a new anti-tumor treatment has not been started, the subject should complete a safety follow-up again at 90 days (±7 days) after the last administration where possible. During this period, subjects are closely observed for adverse events. Adverse events during the study period need to be followed up until the event is resolved, such as recovered, return to baseline, stabilization, or the subject withdraws the informed consent, is lost to follow-up, or dies. If a subject has discontinued treatment and his/her imaging evaluation has not yet reached PD, the subject still needs to undergo tumor response assessments visits every 6 weeks (±7 days) in the first year, and every 12 weeks (±7 days) in the second year and thereafter until PD (imaging evaluation), start of a new anti-tumor treatment, death or loss to follow-up. After the last safety follow-up or the last progressive disease follow-up (whichever occurs later), a survival follow-up should be performed every 3 months (±7 days) until the end of the study, death or loss to follow-up (for subjects without undergoing safety follow-up, the time should be counted from the last visit)

to collect the subjects' subsequent anti-tumor treatment and survival status information. It is allowed to complete such follow-ups by telephone.

The study schedule and procedures are shown in **Table 1**.

3.2 Study Design Principle

3.2.1 Rationale for the study design

As mentioned above, the first-line treatment of PMBCL is based on rituximab combined with chemotherapy, usually with dose-adjusted high-intensity chemotherapy with or without mediastinal radiotherapy, and the treatment regimen is usually R -CHOP or RV/MACOP-B or R-CHOP14 or dose-adjusted R-DA-EPOCH. For first-line treatment-refractory or relapsed PMBCL, traditional palliative treatment has poor efficacy and extremely poor prognosis (the ORR is 0-25%, and the 2-year OS rate is 15%)[7][8][9]. There is currently no unified standard treatment, and generally a regimen without crossover resistance to the prior treatment regimen or participation in clinical trials is selected for patients.

PMBCL is very similar to Hodgkin lymphoma (cHL) in terms of gene expression profile, clinical and biological characteristics, but is significantly different from other types of DLBCL. Relapsed or refractory cHL has a significant increase in PD-1 positive tumor infiltrating T cells. Coupled with 9p24.1 chromosome mutations and high expression of PD-L1, the ORR of PD-1 inhibitor monotherapy can reach 65%-87%, with a median duration of response up to 16 months[12]. The mutation rate of 9p24.1 chromosome in PMBCL is as high as 70%, and multiple studies have shown that it is accompanied by significantly high expression of PD-L1/PD-L2 protein as well as inflammatory infiltration and immune escape mechanism of its tumor microenvironment, all suggesting that immune checkpoint inhibitor therapy may be effective[12].

The efficacy of PD-1 inhibitors in PMBCL has also been verified recently. The phase Ib clinical trial KEYNOTE-013 preliminarily confirmed that pembrolizumab (Keytruda) had demonstrated good efficacy in relapsed or refractory PMBCL. Among 17 patients, the ORR was 41%, the CR rate was 12%, and the other 6 patients had SD (35%)[12]. The results recently released by the phase II clinical trial KEYNOTE-170 (NCT02576990) showed that the median follow-up time was 3.5 months (1 day-22.8 months). The ORR of Keytruda was 45%, of which the CR rate was 11%, and the PR rate was 34%. Among the 24 effective cases, the median time to objective response was 2.8 months. The overall safety profile was good. The US FDA quickly approved Keytruda on June 13, 2018 for the indication of "adults and children with refractory or relapsed PMBCL after second-line and above treatment" based on this study[15].

The investigational drug GB226 is an anti-PD-1 monoclonal antibody molecule, which has the same mechanism of action as nivolumab and pembrolizumab. This trial is designed to confirm the efficacy and safety of GB226 in the treatment of Chinese patients with relapsed or refractory PMBCL. The total response rate, the primary endpoint of the trial, can reflect the anti-tumor activity of the investigational drug. At the same time, there are a series of secondary efficacy endpoints such as duration of response (DOR), time to response (TTR), disease control

rate (DCR), progression-free survival (PFS), and overall survival (OS) to prove the benefits of the investigational drug for Chinese people with the target indications. In addition, the protocol will also closely monitor adverse reactions during treatment to ensure the safety of subjects, and evaluate the safety of GB226 through adverse events collection, laboratory examination, electrocardiogram and other measures, in order to further evaluate the overall safety and tolerability of GB226.

3.2.2 Selection of dose

For the preclinical safety evaluation of GB226, single and multiple-dose toxicity tests were carried out in cynomolgus monkeys. By referring to the preclinical toxicology tests of Keytruda and Opdivo, the maximum tolerated dose (MTD) and no observed advance effect level (NOAEL) of a single administration was 200 mg/kg; after repeated administrations at doses of 10, 30 and 100 mg/kg once a week for 5 times with a recovery period of 8 weeks, the drug exposure at the highest dose was at least 100 times the intended clinical dose, which met the full exposure requirements of toxicity tests. The test results only found a mild and recoverable effect on the thyroid organs, similar to the adverse reactions of similar drugs on the market.

A phase I clinical study of GB226 (Gxplore-001) screened and enrolled histologically or cytologically diagnosed patients with advanced (stage IIIb, stage IIIc, unsuitable for multiple treatments), metastatic (stage IV) or relapsed solid tumors who were inoperable, had failed or could not tolerate systemic treatment, and/or had no effective standard treatment available. The study consisted of a single-dose group and a multiple-dose group, each involving 3 dose groups (1, 3 and 10 mg/kg). The study was divided into a main study phase and a continued treatment phase. Main study phase: in the single-dose group, the subjects were followed up to Week 8 after a single dose; in the multiple-dose group, the subjects were administered every 2 weeks for a total of 6 times, and followed up to Week 12. The primary objective was to evaluate the single-dose and multiple-dose safety and tolerability of GB226 in selected patients with solid tumors and hematological tumors. As of August 31, 2018, a total of 42 subjects had been enrolled, none of them had had DLT, and the highest tolerated dose was 10 mg/kg, with good tolerability in the current phase. The AEs found during the entire study were basically the same as with Opdivo and Keytruda; at the same time, the anti-tumor activity of GB226 was also observed. The preliminary pharmacokinetic results showed that the main PK parameters such as exposure and half-life in the single-dose 3 mg/kg group were close to those of nivolumab 3 mg/kg. The multiple-dose PK data are still being collected. Among the 35 preliminarily efficacy-evaluable subjects, the best response observed was PR in 9 (25.7%) subjects and SD in 15 (42.9%) subjects. Clinical efficacy was observed in different dose groups receiving a single dose and multiple doses. For the similar drugs nivolumab and pembrolizumab of this product, the current clinical dose of nivolumab is 3 mg/kg or 240 mg; the current clinical dose of pembrolizumab is 2 mg/kg or 200 mg. In the early clinical study of nivolumab, the doses of 3 mg/kg and 10 mg/kg were explored. Both dose groups could tolerate the administration. According to the efficacy data, there was no significant difference between the two dose groups. In the early clinical study of pembrolizumab, the doses of 2 mg/kg and 10 mg/kg were explored. The results showed that both doses were well tolerated, and as shown by the efficacy data, there was no

significant difference between the two dose groups. The clinically recommended dose of Opdivo as monotherapy for melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, and classic Hodgkin lymphoma is 3 mg/kg, administered every 2 weeks.

Therefore, the dose of GB226 in this trial is initially determined to be 3 mg/kg, administered every 2 weeks. During treatment, due to the toxicity of the drug, if it is necessary to suspend the medication and terminate the treatment, please refer to Section 5.7.

4 TRIAL POPULATION

4.1 Trial Population and Number of Cases

It is planned to recruit 53 patients diagnosed with relapsed or refractory primary mediastinal large B-cell lymphoma, defined as patients with relapsed or refractory PMBCL who have undergone autologous stem cell transplantation or have failed at least second-line and above systemic treatment. (Relapsed is defined as progressive disease after the tumor has achieved a response following the last systemic treatment; refractory is defined as the tumor failing to achieve CR or PR after the last systemic treatment)

4.2 Inclusion Criteria

Only those who meet all the following criteria can be included in this trial:

1. Aged ≥ 18 years, male or female;
2. Understand the trial procedures and content, and voluntarily sign a written informed consent form;
3. Histopathologically confirmed primary mediastinal large B-cell lymphoma (PMBCL):
    1) Recurrence after autologous hematopoietic stem cell transplant (ASCT), or failure to achieve CR or PR within 60 days after ASCT. If relapsed or refractory patients have received other interventions after ASCT, the disease must become relapsed or refractory after the last systemic treatment; or:
    2) Patients who are not suitable for ASCT must become relapsed or refractory after failure of second-line or above systemic chemotherapy. Local radiotherapy is not considered as a separate first-line treatment;
    3) Before enrollment, the subjects have received adequate treatment with rituximab;
4. Agree to provide archived tumor tissue specimens or fresh tissue samples;
5. ECOG score of 0-1 point;
6. Expected survival ≥ 3 months;
7. The computed tomography scan performed within 28 days before the investigational drug administration should show that there is at least one clearly measurable tumor lesion in two vertical directions (the longest diameter of intranodal lesions >1.5 cm, and the longest diameter of extranodal lesions >1.0 cm (based on the Lugano 2014 criteria);
8. Blood routine requires hemoglobin ≥80 g/L, neutrophils ≥1.0 $\times 10^9$/L, platelets ≥75$\times 10^9$/L (no blood transfusion or use of biological stimulating factors within 14 days before the test);
9. Serum creatinine ≤ 1.5 × ULN or calculated value of creatinine clearance ≥ 50 mL/min (Cockcroft-Gault formula);
10. Total bilirubin ≤1.5 × ULN (for patients with Gilbert syndrome, ≤5 × ULN], aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN (for patients with liver metastases, AST and/or ALT ≤ 5 × ULN));

11. Thyroid function parameters: thyroid-stimulating hormone (TSH) and free thyroxine (FT3/FT4) are in the normal range; if TSH and FT3 are not in the normal range, subjects with FT4 in the normal range can be included;
12. Females who are confirmed to be not pregnant within 7 days before administration; fertile males or females agree to take medically approved effective contraceptive measures during the entire trial period and within 6 months after the end of the trial;
13. Patients can be followed up on schedule, can communicate well with the investigator, and can complete the trial in accordance with the trial procedures.

4.3 Exclusion Criteria

Those who meet one of the following conditions will not be included in this trial.

1. Patients who have previously suffered from other malignancies (except for cured cervical carcinoma in situ and skin basal cell carcinoma or squamous cell carcinoma) shall not participate in the trial unless he/she has had a complete response for at least 5 years before enrollment and is not expected to require any other treatment during the entire trial period;
2. Confirmed lymphoma central nervous system (CNS) infiltration, including brain parenchyma, meningeal invasion, or spinal cord compression etc.;
3. Those who have received systemic chemotherapy or targeted therapy within 2 weeks before the investigational drug administration, or received radical/extensive radiotherapy, anti-tumor biotherapy (tumor vaccine, cytokine or growth factor for the purpose of tumor control) within 4 weeks, or local palliative radiotherapy within 1 week;
4. Those who have received systemically administered corticosteroids (prednisone > 10 mg/day or equivalent dose) within 2 weeks before the investigational drug administration;
5. Those who have undergone autologous hematopoietic stem cell transplantation within 2 months, or allogeneic hematopoietic stem cell transplantation within 5 years before the investigational drug administration;
6. Those who have undergone major surgery under general anesthesia within 4 weeks before the investigational drug administration; or local anesthesia/epidural anesthesia within 2 weeks;
7. Those with a history of active and known autoimmune diseases, including but not limited to systemic lupus erythematosus, psoriasis, rheumatoid arthritis, inflammatory bowel disease, and Hashimoto's thyroiditis, except for type I diabetes, hypothyroidism that can be controlled only by hormone replacement therapy, skin diseases requiring no systemic treatment (e.g., vitiligo, psoriasis), controlled celiac disease, or diseases that are not expected to recur without external stimuli;
8. Uncontrolled hypertension (systolic blood pressure> 140 mmHg and/or diastolic blood pressure> 90 mmHg) or pulmonary hypertension or unstable angina pectoris; myocardial infarction or bypass or stent surgery within 6 months before administration; a history of

New York Heart Association (NYHA) Class 3-4 chronic heart failure; clinically significant valvular disease; severe arrhythmia (excluding atrial fibrillation, paroxysmal supraventricular tachycardia) requiring treatment, including QTc interval ≥450 ms for males and ≥470 ms for females (calculated by Fridericia formula); left ventricular ejection fraction (LVEF) < 50%; cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months before administration;

9. Those complicated with other serious medical diseases, including but not limited to: uncontrolled diabetes, active peptic ulcer, active bleeding, etc.;
10. Those with active infections requiring systemic treatment;
11. Those with past or current active tuberculosis infection;
12. Those who are positive for human immunodeficiency virus antibody (HIV-Ab) and Treponema pallidum antibody (TP-Ab); positive for hepatitis C antibody (HCV-Ab), with hepatitis C virus RNA quantification > the upper limit of normal of the detection unit; positive for hepatitis B virus surface antigen (HBsAg), with hepatitis B virus DNA quantification > the upper limit of normal of the detection unit;
13. Comorbidities that require immunosuppressive therapy, or comorbidities that require systemic treatment at an immunosuppressive dose (prednisone> 10 mg/day or equivalent dose of similar drugs); in the absence of active autoimmune diseases, the inhaled or topical use of steroids or prednisone at a dose > 10 mg/day or equivalent doses of similar drugs is allowed;
14. Adverse reactions caused by previous treatments have not recovered to grade 1 or below (CTCAE V5.0) before medication (except for alopecia and grade 2 neurotoxicity caused by chemotherapeutic drugs);
15. Uncontrollable or significantly symptomatic pleural and abdominal effusion or pericardial effusion;
16. Those who have previously used anti-PD-1 antibody, anti-PD-L1 antibody, anti-PD-L2 antibody or anti-CTLA-4 antibody therapy (or any other antibody that acts on T cell co-stimulation or checkpoint pathways);
17. Those who have used other investigational drugs or investigational devices within 30 days before starting the use of the investigational drug;
18. Those who have used live vaccines or attenuated vaccines within 4 weeks before the investigational drug administration;
19. Those who have a history of drug addiction or drug abuse upon inquiry;
20. Those who have a history of interstitial lung disease;
21. Women who are breastfeeding and unwilling to stop breastfeeding;
22. Known to be allergic to recombinant humanized PD-1 monoclonal antibody or any of its excipients; known to have a history of allergic diseases or be of severe allergic constitution;

23. Patients with insufficient communication, understanding, and cooperation, or poor compliance, who cannot guarantee that they will proceed according to the requirements of the protocol;
24. Those who are considered by the investigator to be unsuitable for participating in this clinical trial due to various other reasons.

4.4 Randomization

This trial does not adopt randomization.

4.5 Blinding

This trial does not adopt blinding.

4.6 Criteria for Subjects to Discontinue Treatment and Withdraw from the Trial

4.6.1 Criteria for subjects to discontinue treatment

If one of the following situations occurs during this trial, the investigator should arrange for the subject to discontinue the trial treatment. The investigator should complete the end of treatment visit assessment specified in the protocol, and ask whether the subject will undergo subsequent safety follow-up and survival follow-up or other visits to be conducted by the investigator as required by the protocol and whether the subject will provide subsequent medical information. Subjects can decide to discontinue the treatment at any time during the study, which will not affect their subsequent follow-up.

1. The subject does not comply with the requirements of the clinical trial protocol seriously;
2. The investigator believes that it is in the subject's best interests to discontinue the investigational drug;
3. Intolerable adverse events occur;
4. There is evidence of confirmed tumor progression.
5. The investigator determines that if the investigational drug treatment continues, the health of the subject will be impaired;
6. During the trial, the patient is pregnant or breastfeeding;
7. If two consecutive doses of GB226 are missed or any medication delay exceeds 4 weeks, the investigator judges that the criteria of discontinue the treatment are met;
8. The subject is lost to follow-up or dies during treatment;
9. The subject or his/her guardian requests discontinuation of treatment;
10. The subject withdraws informed consent;
11. The subject starts a new anti-tumor treatment;
12. The study ends.

4.6.2 Criteria for subject withdrawal from the trial

If one of the following situations occurs during this trial, it will be regarded as subject withdrawal from the trial:

1. The investigator decides not to arrange any subsequent visits for the subject, and not to collect any subsequent medical and survival information.
2. The subject decides to withdraw the informed consent, refuses any subsequent follow-up, and refuses to provide any subsequent medical and survival information.
3. The subject is lost to follow-up or dies.
4. The study ends.

4.6.3 Procedures for subjects to discontinue treatment/withdraw from the trial

Subjects who discontinue treatment at any time need to complete the relevant procedures for the end of treatment visit stipulated in the protocol.

If a subject discontinues treatment for any reason, the investigator should inform the subject to continue to receive subsequent follow-up, including safety follow-up, progressive disease follow-up and survival follow-up, and the results of the discussion should be recorded in the medical history and eCRF. If a subject is lost to follow-up, the investigator should contact the subject or their relatives as much as possible, complete the last assessment, and record the reason for the subject's withdrawal from the trial.

If a subject voluntarily withdraws from the trial, the investigator should request the subject to continue the subsequent follow-up; if the subject refuses, no further collection of relevant data is required.

If a subject discontinues treatment due to an adverse event, the adverse event should be followed up until the event is resolved, such as recovery, return to baseline, stable event, or the subject withdraws informed consent, is lost to follow-up or dies, and recorded in the eCRF.

If a subject who signs the ICF, fully meets the enrollment requirements and is enrolled as an eligible subject withdraws from the trial for whatever reason, there is no need to substitute the subject.

4.7 Early End of the Trial

The study can be terminated prematurely for the following reasons. Premature termination of the study should be approved by the principal investigator and the sponsor in written form; meanwhile, study results should be reported according to protocol requirements.

- The investigator doubts the safety of the drug during the study, and considers continued study may cause serious risk to subjects;
- The principal investigator and the sponsor believe that the number and severity of adverse events require early termination of the trial;
- The efficacy cannot meet expectations, and there is no need to continue the clinical trial;

- Drug regulatory authority cancels the study;
- If the following situations occur, the sponsor has the right to decide to terminate the trial of a certain study site;
  - The study site seriously violates the ICH-GCP;
  - The study site seriously violates the protocol;

After the trial is terminated, all relevant trial records should be kept for future reference.

4.8 End of Trial/Charity Drug Donation

The end of the trial is defined as that the last subject withdraws the informed consent, discontinues the treatment or withdraws from the trial, is lost to follow-up or dies, the treatment has been completed for 2 years, or the study ends early, whichever occurs first.

If a subject is still receiving the study medication at the end of the trial, the investigator believes that the subject will still have clinical benefits based on comprehensive clinical judgment, and there are no drug supply problems and no relevant national laws and regulations are met, after discussion by the investigator and the sponsor, the subject will continue to be given charity drug donation until progressive disease, intolerable toxicity, start of a new anti-tumor therapy, or the subject voluntarily stops the treatment.

During the donation period, drug-related adverse events (AEs) and serious adverse events (SAEs) will be collected continuously, and SAEs will be reported to the sponsor and the safety department. Routine safety monitoring should continue as needed. The investigator will select and schedule test items according to conditions and should preserve relevant documents in the original document. The sponsor will not routinely collect results of these tests. Data collected during drug donation will not be included to statistical analysis of the study.

5 TREATMENT

5.1 Investigational Drug

5.1.1 Dosage form and strength of investigational drug

Generic name: Genolimzumab Injection

English name: Genolimzumab Injection

Trade name: None

Investigational drug code: GB226

Main ingredient: Recombinant humanized anti-PD-1 monoclonal antibody

Description: Colorless to light yellow liquid.

Strength: 70 mg/7 mL/vial

[Shelf life] 24 months tentatively

5.1.2 Formulation and preparation of investigational drug

Genolimzumab Injection is an intravenous injection to be diluted to 1 mg/mL~10 mg/mL with 0.9% sodium chloride solution for intravenous infusion. The formulation and infusion of all patients should be implemented in accordance with this protocol.

Before administration, it is required to visually observe the appearance of the drug product solution for particulate matter and discoloration. Genolimzumab is a colorless to light yellow solution. If the solution is cloudy, discolored, or contains other exogenous particulate matter except for a few transparent to white protein-like particles, this vial should be discarded. Do not shake the vial.

1) Calculate the dosage and determine the number of used vials of this product: Each 7 mL vial of this product contains 70 mg. Calculate the total amount of this product solution that needs to be formulated. For example:

   Body weight (kg) × 3 mg/kg = dosage (mg)

   Dosage/10=volume of drug that needs to be drawn (mL)

   If the subject weighs 62.3 kg and is administered at a dose of 3 mg/kg, the calculated dose is 186.9 mg, and the administration volume is 18.69 mL, which is rounded to one decimal place. Hence, the volume to be drawn is 18.7 mL.

2) Use a syringe to draw the required volume of the drug and add it to 100 mL of 0.9% sodium chloride solution. Gently turn over the infusion bag to prevent air bubbles. Under normal circumstances, it is necessary to expel the corresponding volume of 0.9% sodium chloride solution from 100 mL of 0.9% sodium chloride solution to ensure that the total volume is 100 mL. For example, if the administration volume is 18.7 mL, then 18.7 mL of 0.9% sodium chloride solution needs to be expelled first. The volume of sodium chloride solution mentioned above is only the recommended amount, and can be adjusted according to

the actual situation in clinical operation, but the administration concentration must be strictly controlled within 1 mg/mL-10 mg/mL.

3) The infusion time of GB226 is about 60 minutes (±10 minutes). If no infusion-related adverse reactions occur during the first infusion, the subsequent medication time can be shortened to 30 minutes (±10 minutes).

4) This product has not been tested for physical and biochemical compatibility with any other drugs, and should not be infused with other drugs at the same time.

5) As this product does not contain antibacterial preservatives, in order to prevent infection and protect the safety of subjects, this product should be used immediately after preparation. If it cannot be used immediately, it needs to be stored at 2 ℃-8 ℃, yet no more than 24 hours. At room temperature, it should not be stored for more than 6 hours, including the storage time in the intravenous container and the infusion time. No freezing.

6) After infusion, sterile normal saline must be used to flush the infusion tube.

5.1.3 Administration route

According to the weight of the subject, the corresponding dose of GB226 is formulated in 0.9% sodium chloride injection. The first infusion should be completed within 60 minutes (±10 minutes), and the infusion rate is about 1.6 mL/min. If no infusion-related adverse reactions occur during the first infusion, the subsequent medication time can be shortened to 30 minutes (±10 minutes). During the infusion process, the subject's condition needs to be closely monitored. If an emergency such as allergy occurs, rescue treatment should be given.

Please note: Genolimzumab is strictly prohibited for intravenous bolus injection or infusion without dilution, and the diluted injection cannot be used for intravenous bolus injection, either.

The time of administration and drug label information should be recorded in the subject's original materials or eCRF.

5.1.4 Storage

Genolimzumab Injection should be refrigerated at 2 ℃-8 ℃ and protected from light. The investigational drug should be kept by a dedicated person and locked. The temperature of the refrigerator should be checked and recorded every day. If any malfunction occurs, please report to the sponsor in time. The Investigational Drug Registration Form should be filled out and confirmed by the drug administrator and the investigator each time the drug is distributed and recovered.

All investigational drugs provided by the sponsor can only be used in this trial, and should not be used for purposes other than those specified in this protocol. The investigator must promise not to provide the investigational drug to anyone unrelated to the trial.

If any drug quality problem is found during transportation and storage, please record and report it to the sponsor in time. Drug quality problems may include:

- Investigational drug quality

- The storage temperature exceeds the specified range (2 ℃-8 ℃)
- Vials and packaging box
- Labels

5.1.5 Packaging and labeling

The packaging unit of GB226 is a small box, and each small box contains 1 vial of 70 mg/7 mL injection.

All packages and drug labels contain the following information: investigational drug, drug number, trial protocol number, storage conditions, contents, method of administration, batch number, shelf life and standard text "For clinical trials only". If there are quality problems such as turbidity and precipitation in the injection, please isolate the injection and exchange it for new investigational drug for use.

5.1.6 Counting of drugs

Genor Biopharma Co., Ltd. will record and track the investigational drugs delivered to the study site. The investigator should confirm that the received drug is intact, the quantity is the same as when it is delivered, and the transportation temperature is within the specified range. The transportation conditions should be recorded. After receiving the drugs, the investigator should count the quantity of drugs, and sign the receipt or relevant documents for confirmation. The receipt or related documents should be stored as proof of receipt.

In addition, each study site should fill in the "drug count table" (provided separately) in a timely and accurate manner to ensure that the investigational drug inventory record is correct. The record should include the date of drug receipt, batch number, drug number, quantity distributed, subject number, initials, date of distribution, and signature of the distributor.

Throughout the trial process and before the drug is destroyed, the clinical monitor will be responsible for checking and verifying the investigational drug count table. All used and unused drugs must be kept and counted. With the authorization of the sponsor, the study site can dispose of the used medicine bottles according to the requirements of the regulations and keep the records of destruction. Unused drugs should be returned to Genor Biopharma Co., Ltd. by the monitor. Unused investigational medications should be stored at 2 ℃-8 ℃.

The investigator promises not to provide investigational drugs to patients who are not included in the trial or unauthorized trial personnel.

5.2 Compliance

The investigational drug should be used under the supervision of the principal investigator or the trial nurse. The time and process of the investigational drug infusion should be recorded in the patient's original materials and eCRF.

5.3 Precautions during Infusions

1. Intravenous bolus injection or infusion of Genolimzumab without dilution is strictly prohibited, and the diluted injection cannot be used for intravenous bolus injection, either. The

investigational drug does not contain preservatives, and the principle of aseptic operation should be strictly followed during the preparation of the drug;

2. Before preparing the drug, check whether the drug is within the shelf life and whether the liquid medicine in the vial is clear. If there is precipitation or particulate matter, use another vial of drug instead;
3. The infusion should be carried out by qualified professional medical staff in a ward with perfect first aid measures, and the whole process of infusion should be under the supervision of a clinician;
4. Subjects experiencing infusion reactions should be treated in time. If an infusion reaction occurs, the infusion rate of the subject's subsequent infusions should be reduced to half of the original infusion rate or even lower. Prophylactic antipyretic analgesics (e.g., acetaminophen) and antihistamines (e.g., diphenhydramine) 30-60 minutes before the infusion are recommended to reduce the risk of infusion reactions. Vital signs should be closely monitored during the infusion and within 1 hour after the completion of the infusion;
5. If no significant infusion reaction occurs during the first administration, the subsequent infusions can be shortened to 30 minutes (±10 minutes); after the infusion, the subject should continue to be observed for 1 hour, and can leave only after the investigator judges that there are no abnormal symptoms or signs.

5.4 Missed Doses and Delayed Administration

In the event that a subject fails to take the medication as scheduled in the protocol, the subject should take the medication as soon as possible.

1. If the administration is delayed for 1-7 days (including 7 days) from the planned medication time, the visit and medication should still be carried out according to the original regimen;
2. For the Q2W dosing regimen, if the administration is delayed for more than 7 days from the planned medication time, the administration will be postponed to the time of the next dose. This visit should be recorded as a missed dose, and subsequent administrations should still be carried out according to the original regimen.
3. If there are more than two consecutive missed doses of GB226 or the administration is delayed for more than 4 weeks, and the investigator judges that the criteria for termination of treatment are met, then the subject should terminate the treatment with the investigational drug.

5.5 Concomitant Medication and Prohibited Medication

5.5.1 Concomitant medications/treatments

All concomitant medications and treatments (including over-the-counter drugs) from 28 days before the first study drug administration to 90 days (±7 days) after the last administration or before the start of a new anti-tumor treatment (whichever occurs first) should be collected and

recorded in the eCRF. It is necessary to record in detail the reason for, dosage, method of administration, start date and end date of the concomitant medications and treatments.

Subjects need to be informed that any new drugs, herbs, and food supplements taken or used after the start of the trial must be notified to the study site.

The use of antihypertensive drugs is allowed, but it should be noted that transient hypotension may occur during the infusion of the monoclonal antibody, so subjects can consider suspending antihypertensive drugs 12 hours before the infusion of GB226. In the event of fever, white blood cell or neutrophil increased, clinical symptoms, positive imaging or bacterial culture test and other evidence suggesting infections, routine anti-infective treatments should be given. When immune-related adverse events occur, symptomatic treatment should be actively implemented according to clinical diagnosis and treatment routines. Refer to Table 6 for treatment principles.

During the trial period, all subjects can receive palliative care and supportive care for disease-related symptoms. Palliative (limited range) local radiotherapy for pain relief is allowed, and the site of local radiotherapy should be a non-unique target lesion; the target or non-target lesion receiving local radiotherapy cannot be used for efficacy evaluation; if local radiotherapy is performed during treatment to relieve the pain, for instance, please first assess whether the subject has had progressive disease (PD).

Bisphosphonates can be given to subjects already with bone metastases before enrollment. If increasing the dose of ongoing bisphosphonates is considered due to worsening bone pain or bisphosphonates need to be prescribed, please first assess whether the subject has had progressive disease (PD).

Subjects can use topical, ocular, intra-articular, intranasal, and inhaled corticosteroids. Subjects are allowed to use systemic corticosteroids at physiological replacement doses (ie, prednisone $\leq$ 10 mg/d). The short-term use of corticosteroids is allowed to prevent (e.g., contrast agent allergy) or treat non-autoimmune disorders (e.g., delayed allergic reactions caused by contact allergens), or to treat adverse reactions caused by the study drug.

During the entire trial period, in addition to the investigational drugs, patients should be given the best symptomatic and supportive treatment.

5.5.2 Prohibited medications/treatments

During the clinical trial, it is prohibited to use all biological drugs that may cause immune dysfunction. If a subject has other concomitant disorders, the investigator will determine whether other drugs are allowed, and concomitant drugs should be avoided as much as possible, especially drugs that have a great impact on the judgment of trial results, so as not to affect the judgment of safety and tolerability. During the trial period, if SARs or SAEs occur, or the original condition deteriorates or the participant is complicated with other serious diseases, the investigator should promptly give combination medicine and actively carry out rescue treatment. If a subject meets the criteria for termination of treatment, the subject should be properly arranged for to complete the end of treatment visit and subsequent follow-up.

The following drugs are prohibited during the trial:

1) Any concomitant anti-cancer treatment (chemotherapy, Chinese medicine, immunotherapy, biological products, extensive radiotherapy, hormone therapy, targeted therapy, surgery, interventional device therapy, etc.), investigational treatment or approved treatment;
2) Immunosuppressants, except for such drugs used to treat adverse events and drugs specified in the protocol;
3) Systemic corticosteroids with immunosuppressive effects, and systemic corticosteroids with immunosuppressive effects, except for temporary treatments of infusion reactions and immune-related AEs or hormone replacement therapy for adrenal insufficiency. The dosage of corticosteroids required to control infusion reactions or immune-related AEs should be gradually reduced before the next administration, and the daily dosage should be less than or equal to 10 mg of prednisone or its equivalent. If more than 10 mg of prednisone is used daily, GB226 needs to be suspended;
4) Concomitant drugs (prescription drugs, over-the-counter drugs, or traditional Chinese medicines) are prohibited unless they are permitted by the investigator to treat special clinical events. Subjects are not allowed to use any Chinese medicine that is approved for anti-cancer treatment (it is not allowed to use Chinese medicines with wording like "anti-cancer" or "anti-tumor" in the package insert). If necessary, the investigator can decide to give subjects Chinese medicines that are not for anti-cancer treatment or supportive treatment.
5) The use of live vaccines or attenuated vaccines is prohibited during the study drug treatment period until 5 months after the last administration.
6) Biologics such as colony stimulating factor drugs should be used with caution. It is prohibited to use long-acting preparations of such drugs or use such drugs as prophylactic medications.

If the investigator judges that any other specific anti-cancer treatment is needed, the subject needs to terminate the treatment with the investigational drug.

5.6 Principles of Treatment of Toxic and Side Reactions

Infusion reactions

Before GB226 infusions, it is generally not necessary to use glucocorticoids, antihistamines or antipyretic analgesics for pretreatment, but infusion-related allergic reactions may still occur during the infusion, such as fever, hypothermia, chills, dizziness, urticaria, dyspnea, hypotension and other symptoms. Most of them occur during the first infusion or within 1 hour after the infusion. If an infusion reaction occurs, corresponding prophylaxis and treatment measures can be taken during the infusion and before subsequent infusions. The principles of prevention and treatment of infusion reactions are shown in Table 2.

In order to ensure the safety of subjects during treatment with GB226, the investigator should have first aid equipment and drugs readily available during the administration of GB226, and closely observe the subject's condition; if necessary, the subject should be transferred to the intensive care unit for observation and treatment.

Table 2 Prevention and treatment of infusion reactions

Adverse event	Prevention and treatment recommendations
Mild to moderate allergic reactions after infusion (e.g., urticaria, fever, chills, etc.)	The infusion rate can be reduced. If no drugs to prevent infusion reactions are used before infusion, the subject can be given glucocorticoids, antihistamines, and antipyretic analgesics, and should be closely observed.
Serious allergic reactions (e.g., bronchospasm)	The infusion should be stopped immediately and appropriate treatment measures should be taken. Refer to Appendix 1 Management of Infusion Reactions and Anaphylactic Shock.
The infusion is suspended due to an infusion reaction, but the infusion reaction is not serious enough to require discontinuation of the investigational drug	The infusion can be restarted after the test result of the subject returns to the pre-infusion level, but the infusion rate should be reduced to half of the original rate or even lower

Note: It usually occurs during the infusion or within 1 hour after the end of the infusion.

Immune-related adverse events (irAEs)

If an immune-mediated AE is suspected, the investigator should ensure that the etiological evidence is conclusive or other causes can be ruled out.

For any ≥ Grade 3 or Grade 2 irAE requiring suspension or permanent discontinuation, the investigator should notify the sponsor as soon as possible, and consult the sponsor if necessary.

Based on the severity of the AE, study medication should be suspended and relevant treatments should be given. For subjects using glucocorticoids, after the adverse reaction is improved to Grade 1 or below, the glucocorticoid dose should be gradually reduced and gradually lowered for at least 1 month. If necessary, short-term immunosuppressants such as tumor necrosis factor antagonists, mycophenolate mofetil or other drugs can be used. If the severity of the AE remains at Grade 1 or below, the study medication can be restarted. If an immune-mediated, persistent, worsening, or recurring Grade 3 adverse reaction, or any Grade 4 immune-mediated adverse reaction occurs, the study medication should be permanently discontinued. For the identification, diagnosis and management of irAE and dose adjustment methods, please refer to the clinical guidelines issued by ASCO: ASCO Clinical Practice Guidelines for Management of Immunotherapy-Related Toxicities (2018) for treatment[16]. For details, see Appendix C in Section 15.3.

5.7 Discontinuation and Dose Adjustment

If the subject develops immune-related toxicity, measures for GB226 should be taken in accordance with the following standards, including permanent discontinuation, suspension and continued use of GB226. For further examinations and treatment measures, please refer to the

ASCO Clinical Practice Guidelines for Management of Immunotherapy-Related Toxicities (2018)[16]. For details, please refer to Section 5.6 and Appendix C in Section 15.3.

6 SCHEDULE OF ACTIVITIES

See Figure 4 and Table 1 for the trial visit schedule and procedures.

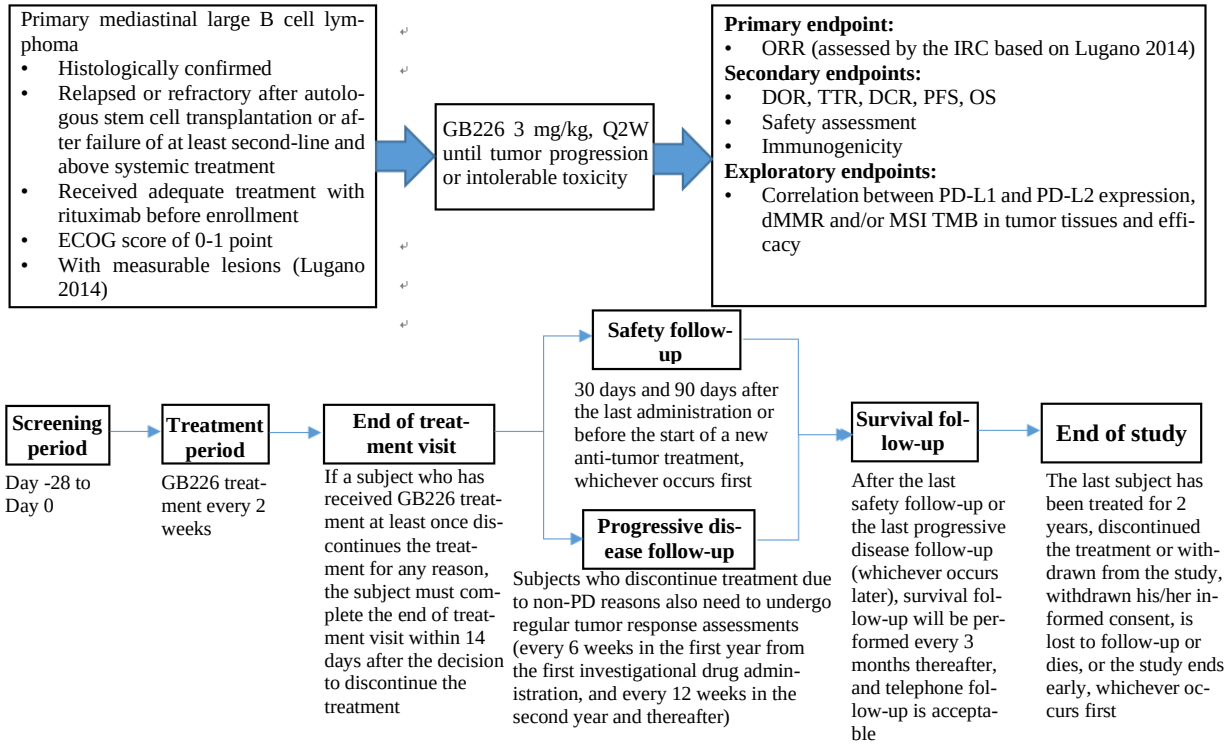

Figure 4 Schedule of Activities

6.1 Screening period

After signing the ICF, subjects enter the trial screening period. According to the time limit for obtaining laboratory test results, the screening period is up to 28 days, during which subjects will complete the assessments during the screening period according to the visit schedule in the schedule of activities (Table 1). Subjects who meet all the inclusion criteria of the trial and do not meet the exclusion criteria will enter the trial treatment period.

All potential subjects will undergo the following procedures and assessments before starting the trial medication:

1) Signing of the informed consent form;
2) Collection of demographic data, inquiry about and review of past medical history, disease and tumor diagnosis and treatment history;
3) Collect information of adverse event;
4) Collect information of concomitant medications.
5) Measurement of height (cm) and weight (kg);
6) Complete physical examination;
7) Eastern Collaborative Oncology Group (ECOG) Performance Status Score;

8) Vital signs;

9) B symptoms;

10) Electrocardiogram;

11) Echocardiography;

12) For imaging examinations (PET-CT and enhanced CT/MRI) and baseline tumor assessments, the International Working Group (IWG)'s response criteria for non-Hodgkin lymphomas and its amendment (2014 Lugano Classification) will be used for initial evaluation and staging of lymphomas. The imaging examination should include both PET-CT and diagnostically valuable enhanced CT/MRI examinations of the neck, chest, abdomen and pelvis. If there are special clinical indications, a head MRI examination is also required. If any site of possible bone metastasis suggested by PET-CT is not covered by conventional examinations, CT or X-ray should be used to confirm the location of the disease, and later the disease should be followed up with the same scanning method. Imaging examinations that are routinely performed for clinical diagnosis and treatment can be used as screening examinations, provided that they meet the diagnostic quality requirements and have been performed within 28 days before the first administration;

13) Collection of archived tumor tissue paraffin section specimens or fresh tissue specimens;

14) Bone marrow aspiration/biopsy: During the screening period, combined with the subject's clinical symptoms and the results of laboratory tests and PET-CT examinations, the investigator will decide whether to complete this examination. The examination results of diagnostic quality within 2 weeks before the signing of the ICF are acceptable.

15) Laboratory tests:

- Blood routine
- Urine and stool routine
- Blood biochemistry
- LDH and β2 microglobulin
- Thyroid function
- Screening tests for TP-Ab, HCV-Ab, HIV-Ab, and HBsAg
- If HBsAg is positive, a HBV-DNA quantitative test is required; if HCV-Ab is positive, a HCV-RNA quantitative test is also required

16) Pregnancy test: For women of childbearing age who are not postmenopausal or have not undergone surgical sterilization, a serum β-human chorionic gonadotropin (β-hCG) pregnancy test is required;

17) Analysis of biomarkers:

- Expression of PD-L1 and PD-L2 in tumor tissues

- Mismatch repair deficiency (dMMR) and/or microsatellite instability (MSI)
- Tumor mutation burden (TMB)
- Immune cell typing and cytokines

During the screening period, all laboratory tests, physical examinations, weight, vital signs, electrocardiogram, and ECOG performance status score should be completed within 7 days before the first administration of investigational drug.

After obtaining all the screening and baseline examination results, the subject eligibility for inclusion in the trial should be confirmed according to the content of the subject's enrollment review form; once a subject meets the requirements for inclusion, the subject will be assigned a subject number, which is the unique number to identify the subject and remains unchanged throughout the trial.

6.2 Treatment Period

From the first administration to the end of treatment visit, subjects will receive a trial medication every 2 weeks (±3 days) and a tumor efficacy evaluation every 6 weeks (±7 days) in the first year and every 12 weeks (±7 days) in the second year and thereafter (the interval between the first efficacy evaluation and the first administration of the investigational drug must be ≥6 weeks, except for cases where progressive disease is considered).

The examinations and assessments that the subjects need to complete at each visit include:

1) General conditions, concomitant medications and adverse events: Recorded at visits every 2 weeks (±3 days);
2) Weight, physical examination, vital signs, and ECOG performance score: Recorded at visits every 2 weeks (±3 days);
3) ECG examination: Before administration every 2 weeks (±3 days), until the treatment is terminated; during the treatment, if necessary, the ECG should be monitored at any time. If there is any heart discomfort or abnormal electrocardiogram, an echocardiography can be additionally performed;
4) Laboratory tests:
    - Blood routine and urine routine: Tested every 2 weeks (± 3 days) before administration until the treatment is terminated;
    - Stool routine: It is not mandatorily required during the treatment period, and can be tested at any time if necessary;
    - Blood biochemistry, LDH, β2 microglobulin, and thyroid function: Tested every 4 weeks (±3 days) before administration until the treatment is terminated;
5) B symptoms: Recorded at visits every 2 weeks (±3 days);
6) Bone marrow aspiration/biopsy: Patients with positive bone marrow examinations during the screening period need to be re-examined when the subsequent efficacy evaluation is

CR or when a bone marrow lesion is suspected to be new or recurring. During the treatment period, the investigator can decide whether to perform bone marrow aspiration/biopsy and its frequency according to the diagnosis and treatment routines.

7) Imaging examination (PET-CT and enhanced CT/MRI) and tumor efficacy evaluation: During the treatment period, a diagnostically valuable enhanced CT/MRI examination of the neck, chest, abdomen and pelvis will be performed every 6 weeks (±7 days) in the first year and every 12 weeks (±7 days) in the second year and thereafter until progressive disease, start of a new antitumor treatment, loss to follow-up or death; throughout the trial period, subjects should use the same imaging technique. At the end of treatment visit after Week 13 and Week 19, a PET-CT examination must be additionally performed for imaging assessment; at other time points, if the investigator judges that the addition of PET-CT examination is more conducive to the accurate evaluation of efficacy, a PET-CT examination can be performed with the consent of the sponsor. The time for imaging examinations should follow the calendar day, and should not be adjusted according to the delay in the start of the cycle or the extension of the treatment cycle. After evidence of progression (if the subject is clinically stable) or response that meets the definition of Lugano criteria, repeat examinations are required at the next evaluation time point to confirm the efficacy.
8) Immune cell typing and cytokines: Tested before administration at Weeks 5, 9 and 13 (± 3 days);
9) Anti-drug antibody (ADA) analysis: Within 1 hour before the first administration, and within 24 hours before administration every 4 weeks (± 3 days) thereafter until the treatment is terminated;
10) GB226 treatment: received once every 2 weeks (±3 days) after the first administration, until confirmed progressive disease, intolerable toxicity, withdrawal of informed consent, start of other anti-tumor treatment, loss to follow-up or death, treatment discontinuation at the discretion of the investigator or subject, or end of the trial.

6.3 End of Treatment Visit

If a subject who has received GB226 treatment at least once decides to discontinue the investigational drug for any reason, the subject should complete the end of treatment visit as soon as possible within 14 days after deciding to discontinue the treatment (the examination results after the last treatment within the past 14 days are acceptable). The following assessments should be completed:

1) Physical examination;
2) Vital signs;
3) Recording of body weight;
4) ECG examinations: An echocardiography can be additionally performed if there is any abnormality;
5) Assessment and recording of the ECOG performance status;

6) Collect information of adverse event;
7) Collect information of concomitant medications;
8) Assessment of B symptoms;
9) Imaging examination (PET-CT or enhanced CT/MRI) and tumor efficacy evaluation: For subjects who have discontinued treatment due to non-PD reasons, have exceeded the prescribed time interval since the time point of the most recent efficacy evaluation specified in the protocol, and have not yet started any subsequent anti-tumor treatment, the efficacy evaluation should be completed at the end of treatment visit as much as possible. At the end of treatment visit after Week 13 and Week 19, a PET-CT examination should be additionally performed;
10) Laboratory tests
    - Blood routine, urine routine and stool routine
    - Blood biochemistry
    - LDH and β2 microglobulin
    - Thyroid function
    - Pregnancy test: For women of childbearing age who are not postmenopausal or have not undergone surgical sterilization, serum β-hCG testing is required
11) Anti-drug antibody (ADA) detection and analysis.

6.4 Follow-up Period

6.4.1 Safety follow-up

All subjects who have received GB226 treatment at least once will undergo a safety follow-up at 30 days (±7 days) after the last administration or before starting a new anti-tumor treatment (if this follow-up overlaps with the end of treatment visit, there is no need to repeat the examinations), whichever occurs first. If a new anti-tumor treatment has not been started, the subject should complete a safety follow-up again at 90 days (±7 days) after the last administration where possible, including the following procedures and assessments:

1) Physical examination;
2) Vital signs;
3) Recording of body weight (kg);
4) ECG examinations: An echocardiography can be additionally performed if there is any abnormality;
5) Assessment and recording of the ECOG performance status;
6) Collect information of adverse event;
7) Collect information of concomitant medications;

8) B symptoms;

9) Laboratory tests:

- Blood routine, urine routine and stool routine
- Blood biochemistry and LDH, β-microglobulin
- Thyroid function
- Pregnancy test: For women of childbearing age who are not postmenopausal or have not undergone surgical sterilization, serum β-hCG testing is required

10) Recording of subsequent anti-tumor treatment for the diagnosed primary mediastinal large B-cell lymphoma (if applicable);

11) Recording of the date of loss to follow-up or death (if applicable).

6.4.2 Progressive disease follow-up

Subjects who have not yet experienced confirmed progressive disease after the end of treatment and have not started any subsequent anti-tumor treatment will continue to be followed up for progressive disease every 6 weeks (±7 days) in the first year from the first administration of the investigational drug, and every 12 weeks (±7 days) in the second year and thereafter until the subject has PD, starts a subsequent anti-tumor treatment, dies or is lost to follow-up, including the following procedures and assessments:

1) Imaging examination (enhanced CT/MRI) and tumor efficacy evaluation: The same imaging techniques as for baseline tumor evaluation should be used;

2) ECOG performance status score, vital signs and physical examination;

3) Adverse events collected up to 90 days after the last dose of GB226 need to be followed up until the event is resolved, such as recovery, return to baseline, or stable event. AEs and SAEs related to the investigational drug need to be collected up to 90 days after the last dose of GB226;

4) Recording of subsequent anti-tumor treatment (if applicable);

5) Recording of the date of loss to follow-up or death (if applicable).

6.4.3 Survival follow-up

All subjects who have received GB226 treatment at least once are required to undergo survival follow-up. These visits are planned every 3 months (±7 days) after the last safety follow-up or the last progressive disease follow-up (whichever occurs later). If the subject has not undergone safety follow-up, the time should be counted from the last visit. The follow-up can be conducted by telephone to collect the subjects' subsequent anti-tumor treatment and survival status information after safety follow-up until the end of the study, death or loss to follow-up. The following procedures/assessments should be performed at each survival follow-up:

1) Adverse event collected up to the safety follow-up period need to be followed up until the event is resolved, such as recovery, return to baseline, or stable event. AEs and SAEs related to the investigational drug need to be collected up to 90 days after the last dose of GB226 (if applicable);
2) Recording of subsequent treatment for the primary mediastinal large B-cell lymphoma (if applicable);
3) Recording of the date of loss to follow-up or death (if applicable).

6.5 Unscheduled Follow-up

If there are hidden safety hazards or clinical symptoms suggesting progressive disease during the treatment, the investigator can arrange corresponding unscheduled follow-ups for further examinations and assessments if necessary.

7 EVALUATION MEASURES OF THE STUDY

7.1 Demographic and Baseline Characteristics

Demographic characteristics

Including gender, age, height, weight, ethnicity and other information.

Previous anti-tumor treatment history

Collection of the pathological diagnosis and classification of primary mediastinal large B-cell lymphoma, date of diagnosis, and prior treatment (drugs or hematopoietic stem cell transplantation, etc.);

Medical history

Collection of other concomitant disorders and treatment history, surgical history not related to the disease, history of allergies, history of trauma, etc.

Concomitant medication/treatment

Concomitant medications or concomitant treatments include over-the-counter drugs, prescription drugs and treatment measures. The concomitantly used prescription drugs or over-the-counter drugs (including concomitant medications for the treatment of adverse events) and any treatment measures should be recorded during the period from 28 days before the first administration of the investigational drug to 90 days after the last dose or before the start of a new anti-tumor treatment (whichever occurs first).

Pathological reconfirmation and biomarker testing of primary mediastinal large B-cell lymphoma (PMBCL)

During the screening period, subjects who are histopathologically diagnosed with PMBCL by the study site and meet the inclusion/exclusion criteria will be included in this trial. The study site will provide the tissue specimens (stained sections, unstained slices or wax blocks, according to actual needs) of the subjects used for pathological diagnosis to the Pathology Center Laboratory for histopathological diagnosis and confirmation, and the study site should cooperate with such provision.

The pathological diagnosis results of the Pathology Center Laboratory are only used for the confirmation of the enrolled population, and not used as the basis for the screening and enrollment of subjects.

If the diagnosis result of the Pathology Central Laboratory is inconsistent with the diagnosis result of the study site, the results should be sent to a third-party pathology consultation center recognized by both parties for judgment. If two of the study site, the Pathology Central Laboratory and the third-party pathology consultation center reached an agreement on the diagnosis result, then this diagnosis will be the final result.

Archived tumor tissue specimens or fresh tissue of subjects must be sent to the central laboratory for biomarker testing.

The above specific procedures will be clearly described in the standard operating procedures (SOP) of the central laboratory.

7.2 Efficacy Variables

7.2.1 Efficacy evaluation criteria

Imaging examination

Subjects will undergo an imaging tumor assessment every 6 weeks (±7 days) in the first year, and every 12 weeks (±7 days) in the second year and thereafter (the interval between the first efficacy evaluation and the first administration of the investigational drug must be ≥6 weeks, except for cases where progressive disease is considered). The positron emission computed tomography (PET-CT) or electronic computed tomography (CT) enhancement technology/magnetic resonance imaging (MRI) will be used to identify lymphoma lesions. If the subject is allergic to CT contrast agents, plain chest CT scans can be used. For areas such as the neck, abdomen, pelvis and mediastinum, enhanced MRI or CT scan can be used. A copy of the imaging examination results should be sent to the Independent Review Committee (IRC) to evaluate the efficacy.

The study stipulates that the baseline imaging assessments during the screening period should include both PET-CT and diagnostically valuable enhanced CT/MRI examinations of the neck, chest, abdomen and pelvis. If there are special clinical indications, a head MRI examination is also required. If any site of possible bone metastasis suggested by PET-CT is not covered by conventional examinations, CT or X-ray should be used to confirm the location of the disease, and later the disease should be followed up with the same scanning method. Imaging examinations that are routinely performed for clinical diagnosis and treatment can be used as screening examinations, provided that they meet the diagnostic quality requirements and have been performed within 28 days before the first administration. CT or MRI examinations will be performed for imaging assessments every 6 weeks during the trial, and the subjects should be examined with the same imaging techniques during the entire study period. It is recommended that at the end of treatment visit after Week 13 and Week 19, a PET-CT examination must be additionally performed for imaging assessment; for efficacy evaluations at other time points, if the investigator judges that the addition of PET-CT examination is more conducive to the accurate evaluation of efficacy, a PET-CT examination can be performed with the consent of the sponsor. The time for imaging examinations should follow the calendar day, and should not be adjusted according to the delay in the start of the cycle or the extension of the treatment cycle. After evidence of progression (if the subject is clinically stable) or response that meets the definition of Lugano 2014 criteria is obtained for the first time, an examination should be repeated at the next evaluation time point (at least 4 weeks later) to confirm the efficacy.

Tumor assessment and examination methods during the trial:

- Enhanced CT: For subjects allergic to contrast agents, enhanced MRI or CT plain scan can be used;

- PET-CT: It is an important auxiliary test for routine screening, baseline tumor assessments, and at the end of treatment visit after Week 13 and Week 19;
- Head MRI: A head MRI can be performed as clinically needed on subjects who have special clinical indications during the screening period or the trial process;
- X-rays are only used as a means of detecting non-target lesions in bone, chest and other parts.

Response evaluation

The efficacy evaluation is conducted by the Independent Review Committee (IRC) in parallel with the investigator, using the International Working Group (IWC)'s 2014 Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification for baseline and follow-up efficacy evaluations of lymphomas[19] (for evaluation methods, refer to Appendix B in Section 15.3). At the same time, the 2016 LYRIC[17] (Lymphoma Response to Immunomodulatory Therapy Criteria) (modified Lugano criteria for immunotherapy) will also be exploratorily adopted.

More and more evidences show that the objective response to immunotherapy may be delayed by several weeks or months, and before that, there may be evident imaging progression or new lesions or some lesions increasing while some target lesions shrinking. When evaluating the efficacy, the investigator should take into account that some subjects may experience temporary tumor flare and pseudoprogression in the first few months after starting immunotherapy, and then the disease will be relieved. Therefore, it is allowed that after a clinically stable subject has the first progressive disease (PD), if the investigator believes that the subject may obtain clinical benefits from continued treatment, the subject can continue to receive treatment, and undergo tumor evaluation again to confirm efficacy at efficacy evaluation time points thereafter by referring to the 2016 LYRIC[17].

If the subject is reconfirmed to have PD according to the LYRIC, and the investigator judges that there is no clinical benefit, the investigator should collect data and perform survival visit according to the requirements for visits at early withdrawal from the trial treatment; if the subject is confirmed to have non-PD, the subject should continue treatment and follow-up according to the visit schedule.

Temporary tumor flare and pseudoprogression may include any of the following conditions:

1) Within 12 weeks of treatment, the total tumor burden increases by ≥50% (based on the SPD of 6 measurable lesions) and is clinically stable;
2) At any point in the treatment, the total tumor burden increases by < 50% (based on the SPD of 6 measurable lesions), but a new lesion appears or the PPD of any old lesion increases by ≥50%;
3) PET-CT shows increased FDG uptake in one or more lesions, but the corresponding lesion volume has not increased, nor the number of lesions.

Definition of clinically stable:

1) No clinically significant symptoms and signs that indicate progressive disease (including deterioration of laboratory test values)
2) No decease in ECOG performance status score
3) No rapid progressive disease
4) No progressive tumors (e.g., spinal cord compression) that require other urgent medical interventions in important anatomical parts

Subjects judged to be clinically unstable should terminate the trial treatment after the first imaging PD evaluated by the investigator, and there is no need to repeat the imaging examination to confirm PD.

7.2.2 Trial endpoints and evaluation measures

Primary endpoint and its evaluation measure

- **Overall response rate (ORR)** refers to the proportion of subjects who achieve complete response (CR) or partial response (PR) as radiographically evaluated by the IRC based on the Lugano 2014 criteria. The first CR or PR should be confirmed after at least 4 weeks.

Secondary endpoints and evaluation measures

- **Duration of response (DOR)** refers to the time from the first CR or PR through tumor assessment to the first progressive disease (PD) or death due to any cause. Immune-related DOR refers to the time from the first CR or PR through tumor assessment to the confirmed progressive disease (PD) (excluding pseudoprogression and reconfirmed as PD) or death due to any cause. Subjects whose progression or death is unknown will be censored at the time of the last valid assessment for DOR.
- **Time to response (TTR)** refers to the time from the first treatment with the investigational drug to the first CR or PR through tumor assessment. Subjects who not experience CR or PR before the data collection cutoff will be censored at the time of the last valid assessment for TTR.
- **Disease control rate (DCR)** refers to the proportion of subjects who achieve CR, PR, and stable disease (SD) through imaging evaluation.
- **Progression-free survival (PFS)** refers to the time from the first treatment with the investigational drug to progressive disease (PD) or to death of the subject due to any cause. Immune-related PFS refers to the time from the first treatment with the investigational drug to the appearance of confirmed progressive disease (PD) (excluding pseudoprogression and reconfirmed as PD) or until the subject's death due to any reason. For subjects whose progression or death is unknown, disease-free survival is censored at the time of the last effective evaluation.
- **Overall survival (OS)** refers to the time from the first treatment with the investigational drug to death due to any cause (or to the last follow-up for patients who are lost to follow-

up). For subjects without death at the last survival visit or before the data collection cutoff will be censored at the time of the last survival visit for OS.

Exploratory endpoint and evaluation measure

- The quantitative values (cut-off value) of programmed cell death protein ligand-1 (PD-L1), programmed cell death protein ligand-2 (PD-L2), and deficient mismatch repair genes (dMMR) and/or microsatellite instability (MSI) and tumor mutation burden (TMB);
- Immune cell typing and counting (B lymphocytes [B lymphocytes [CD19+], T lymphocytes [CD3+] and its subtypes [CD4+ and CD8+ T cells], NK/T cells [CD16+CD56+]), and cytokines (IL-2, IL-6, IL-8, TNFα and INFγ).

7.3 Safety Evaluation

7.3.1 Criteria for safety evaluation measures

Safety evaluations include changes in laboratory tests such as blood routine, clinical biochemistry, thyroid function, urine routine and stool routine, vital signs, physical examination, electrocardiogram, and assessments of symptoms/adverse events.

Adverse events (AEs)

The definition of adverse events is shown in Section 88, and the National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 5.0 will be used for grading of AEs. The investigator should promptly take corresponding treatment measures for adverse events that occur.

Complete physical examination

Including general conditions, skin, lymph nodes, eyes, ears, nose, mouth, throat, neck, thyroid, chest, lungs, cardiovascular, abdomen, limbs, musculoskeletal and specialist examinations, etc. A comprehensive physical examination only needs to be performed during the screening period, including a complete skin examination. Attention should be paid to areas with lymph nodes, including Waldeyer's ring, as well as liver and spleen size and nasopharyngeal examinations. During subsequent follow-ups, physical examinations of the corresponding parts can be performed according to the changes in symptoms and signs.

Vital signs

Vital signs include body temperature, blood pressure, respiratory rate, and pulse.

The Eastern Cooperative Oncology Group [ECOG] performance status score is adopted.

ECOG scoring standard: 0 points: fully active able to carry out all pre-disease function without restriction; 1 point: restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work); 2 points: ambulatory and capable of all self-care but unable to carry out work activities. Up and about <50% waking hours; 3 points: capable of only limited self-care. Confined to bed or chair >50% waking hours; 4 points: completely disabled. Cannot carry out any activities of self-care. Fully confined to bed or chair; 5 points: death.

Laboratory tests

See Table 3 for various parameters of laboratory tests.

Table 3 Various parameter of laboratory tests

Laboratory tests	Specimen	Test parameter
Blood routine	Venous whole blood	Red blood cells, hemoglobin, white blood cells, platelet count, differential blood cell counts (neutrophils, lymphocytes, monocytes, basophils and eosinophils), hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC)
Clinical chemistry	Serum	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltranspeptidase (GGT), alkaline phosphatase (ALP), creatine kinase (CK), total bilirubin (TBIL), direct bilirubin (DBIL), total protein (TP), albumin (ALB), globulin (GLB), urea (BU)/urea nitrogen (BUN), creatinine (Cr), uric acid (Ua), sodium (Na), potassium (K), chlorine (Cl), magnesium (Mg), phosphorus (P), calcium (Ca), fasting blood glucose (GLU)
Tumor indicators	Serum	LDH and β-microglobulin
Urine routine	MSU	Urine pH, urine protein (PRO), urine red blood cells (BLD), urine white blood cells (LEU), urine glucose (GLU), urine bilirubin (BIL), urine ketone bodies (KET), urine specific gravity (SG), urobilinogen (UBG), urine nitrite (NIT).
Stool routine	Stool	Including occult blood test (OB), presence or absence of red blood cells and white blood cells
Thyroid function	Serum	Free thyroxine (FT3/FT4), thyroid stimulating hormone (TSH)
Pregnancy test	Serum	β-human chorionic gonadotropin (β-HCG)

Electrocardiogram

Including heart rate, RR interval, PR interval, QTc interval, QRS wave and other parameters.

Echocardiography

Detect the organic structure inside the heart cavity (e.g., the size of the heart, the area of the heart valve, etc.), the condition of the pericardium, the blood flow of the heart (left and right coronary arteries), and the left ventricular ejection fraction (LVEF).

Bone marrow aspiration/bone marrow biopsy

During the screening period, based on the subject's clinical symptoms and results of laboratory tests and PET-CT examinations, the investigator will decide whether to complete a bone marrow aspiration/biopsy. The examination results of diagnostic quality within 2 weeks before the signing of the ICF are acceptable. Patients with positive bone marrow examinations during the screening period need to be re-examined when the subsequent efficacy evaluation is CR or when a bone marrow lesion is suspected to be new or recurring. After GB226 treatment, the investigator can decide whether to perform bone marrow aspiration/biopsy and its frequency

according to the diagnosis and treatment routines. The protocol does not provide special stipulations. The pathological examination of bone marrow aspiration/bone marrow biopsy should be completed in the laboratory of the study site.

7.3.2 Definition of safety evaluation measures

- Incidence and severity of adverse events/serious adverse events
- Compared with baseline values, changes in laboratory test results, physical examination, electrocardiogram, and vital signs

7.4 Evaluation of Anti-drug Antibodies (ADA)

7.4.1 Analysis of anti-GB226 antibodies

Anti-GB226 antibodies (ADA) in the serum will be analyzed by LBA method. The analysis of anti-GB226 antibodies will be completed by the central laboratory, and the test method should have been validated.

Blood samples for anti-drug antibody analysis should be collected intravenously within 1 hour before the first administration, within 24 hours before administration every 4 weeks, and at the end of treatment visit. The actual blood collection date and time should be recorded in the eCRF.

For the methods and details of blood sample collection, processing, labeling, storage and transportation, please refer to the Central Laboratory Manual which will be received by each study site before the trial starts.

7.4.2 Definition of indicators for anti-drug antibody evaluation

- The number and percentage of patients who develop anti-GB226 antibodies (ADA).

7.5 Evaluation of Biomarkers

7.5.1 Tumor biomarkers

Detect PD-L1 and PD-L2 protein expression, mismatch repair deficiency (dMMR) and/or microsatellite instability (MSI), tumor mutation burden (TMB) in tumor tissues of patients with primary mediastinal large B-cell lymphoma before treatment to assess the relationship between biomarkers and clinical efficacy.

For the collection, processing, storage and transportation of tumor tissue samples and blood samples of PD-L1, PD-L2, MSI and/or dMMR and TMB biomarkers, please refer to the corresponding Central Laboratory Manual. If the subject's tissue samples are insufficient, the collection of tissue samples for PD-L1 and PD-L2 testing should be guaranteed.

7.5.2 Immune cell typing and cytokines

Immune cell typing and counting include B lymphocytes [CD19+], T lymphocytes (CD3+) and their subtypes (CD4+, CD8+) and NK cells [CD16+CD56+], which will be tested in the study site's laboratory within 7 days before the first administration and before administration at

Weeks 5, 9, and 13 (± 3 days). If the study site is not capable of testing, fresh anticoagulated whole blood should be sent to the central laboratory for testing within 24 hours.

Cytokine testing includes interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor α (TNFα) and interferon γ (INFγ), respectively, which should be tested in the study site's laboratory within 7 days before the first administration, and before administration at Weeks 5, 9, and 13 (± 3 days). If the study site is incapable of such testing, serum must be sent to the central laboratory for testing.

8 ADVERSE EVENTS

8.1 Adverse event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the investigational drug. Any new disease or aggravation of an existing disease (e.g., increased frequency or nature), clinically significant abnormality in laboratory test values or other clinical test results, repeated occurrences of an intermittent medical condition that did not appear at baseline e.g., headache), and other medical events (e.g., accidents and other injuries).

If an elective surgery/treatment is scheduled before the trial, then such elective surgery/treatment will not be considered an adverse event in the trial. However, if the condition of the existing disease deteriorates (e.g., requiring surgery/treatment earlier than originally planned) in the trial, then the elective surgery/treatment required due to the deterioration of the disease will be considered an adverse event. Adverse events that occur in the trial should be filled out in the eCRF. The severity of the adverse events should be classified as described in Section 8.1.1 and recorded in the eCRF. The correlation of adverse events and treatment should also be evaluated.

8.1.1 Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 5.0 will be used for grading of AEs.

8.1.2 Correlation

The investigator will use "definitely related", "possibly related", "possibly unrelated", "definitely unrelated" and "uncertain" to evaluate the correlation between adverse events and the investigational drug. The judgment criteria are shown in Table 4 below.

Table 4 Determination for correlation between an AE and the investigational drug

Correlation	Correlation judgment criteria
Definitely related	There is a strong temporal relationship between the adverse event and the investigational drug. The adverse event is in line with the known adverse reaction types of the trial medication and cannot be explained by other causes. The adverse event mitigates or disappears after the investigational drug is reduced or stopped; again; re-administration can cause the adverse event.
Possibly related	There is a strong temporal relationship between the adverse event and the investigational drug. The adverse event is in line with the known adverse reaction types of the trial medication. The disease state or other treatments of the patient may also cause the adverse event.

Possibly unrelated	There is little or no temporal relationship between the adverse event and the investigational drug. The adverse event is not much in line with the known adverse reaction types of the trial medication. The disease state or other treatment modalities of the patient may also cause the adverse event.
Definitely unrelated	There is no temporal relationship between the adverse event and the investigational drug. The adverse event is in line with the known adverse reaction types of non-trial medications. The disease state or other treatment modalities of the patient may also cause the adverse event, and the adverse event can mitigate or disappear after the disease state is improved or other treatment modalities are stopped. The adverse event recurs in the event of repeated use of other treatment modalities.
Uncertain	The relationship between the adverse event and the investigational drug is unclear. The adverse event is similar to the known adverse reaction types of the trial medication. The disease state or other treatment modalities of the patient may also cause the adverse event.

If the investigator believes that the correlation between the adverse event and the investigational drug is possibly related, possibly unrelated, definitely unrelated or uncertain, the investigator should provide other possible causes of the adverse event.

8.1.3 Serious adverse event

If the adverse event meets any of the following criteria, the investigator should report it to the sponsor within 24 hours after confirming it as a serious adverse event.

Table 5 Classification and definition of serious adverse events

Dead	The adverse event leads to death of the subject (death caused by disease progression can be exempt from death reporting)
Life-threatening	The investigator believes that if medical measures are not taken, the adverse event may cause the subject's immediate death, rather than assuming that the adverse event may lead to death or worsening of the condition.
Hospitalized	The adverse event leads to hospitalization, excluding emergency or outpatient visits.
Prolonged hospitalization	Adverse event that occurs during hospitalization and prolongs the existing hospitalization.
Congenital abnormality	Congenital anomaly/birth defect or any malformation resulting in abortion.
Persistent or significant disability or incapacity	AE results in substantial harm to the subject's capacity of conducting daily lives. Incapacity does not include medical events with secondary clinical significance, such as headache, nausea, vomiting, diarrhea, influenza, accidental trauma (e.g. ankle strain).
Significant medical events that require medication or surgery to prevent serious consequences	An important medical event may not cause immediate risk of life, result in death or hospitalization; however, it may jeopardize the subjects or require drug or surgical treatment to prevent the occurrence of the above-mentioned outcomes (death of subjects, life-threatening, result in hospitalization and prolonged hospitalization, and congenital malformation). Such events may include allergic bronchospasm that requires treatment in the emergency room and at home, convulsions that do not require hospitalization, or drug dependence or abuse.

Severe adverse events are determined in terms of severity. A severe adverse event is not necessarily a serious adverse event. For example, vomiting for several hours can be judged as severe, but it is not a clinically serious event.

8.1.4 Treatment and follow-up of AEs

Adverse events determined to be related to the study drug should be followed up to return to baseline level or stabilization. If an adverse event cannot return to the baseline level or stabilization, a reasonable explanation should be recorded in the eCRF.

According to the frequency observed in clinical practice, irAEs are divided into two categories: common (dermatological disorders, gastrointestinal disorders, endocrine disorders, respiratory system disorders and rheumatism/musculoskeletal disorders, etc.) and rare (cardiovascular, vascular, renal, nervous system and eye disorders). Some patients will have infusion reactions. See Table 6 for details.

Table 6 Summary of the frequency of immune-related toxic and side reactions and infusion reactions

Immune-related toxicity (common)	
Immune-related skin toxicity	Maculopapular rash and pruritus are common reactions of immune checkpoint inhibitors (ICI). Lichenification, eczematoid dermatitis and bullous dermatitis and psoriasis have also been reported, but they are less common. Skin toxicity (all grades) has been reported in 30%-40% of patients treated with PD-1/PD-L1 inhibitors. Rash or pruritus (all grades) has occurred in 13%-20% of patients treated with pembrolizumab or nivolumab.
Immune-related gastrointestinal toxicity	Diarrhea is the most common manifestation of immune-related colitis. Diarrhea occurs after an average of 3 infusions, and may also occur immediately after the first infusion. It is reported that the incidence of diarrhea in patients treated with anti-PD-1 monotherapy is ≤19%.
	With an incidence of about 5%, hepatitis in patients receiving anti-PD-1 therapy usually exhibits no significant clinical symptoms, and is characterized by ALT or AST increased, with or without bilirubin increased.
Immune-related endocrine toxicity	The two most common endocrine and immune-related adverse events are hypopituitarism caused by acute pituitary inflammation (central hypothyroidism, central adrenal insufficiency, hypogonadotropic hypogonadism) and abnormal thyroid function (hypothyroidism, hyperthyroidism and thyroiditis). The former has an incidence of ≤13% in patients treated with ipilimumab combined with nivolumab, and the latter has been reported with an incidence of 6%-20% in large phase III clinical trials. Other endocrine disorders, such as primary adrenal insufficiency, type 1 diabetes, hypercalcemia, and hypoparathyroidism have also been reported, but they are less common.
Immune-related pulmonary toxicity	The overall incidence of pneumonia associated with PD-1/PDL-1 and CTLA-4 inhibitor treatment is <5%, and the incidence of high grades (≥Grade 3) is 1-2%. Pneumonia is one of the most common causes of ICI-related deaths. With the expansion of ICI treatment indications and the implementation of more complex regimens, the incidence of pneumonia is also increasing. Studies have shown that compared with PD-L1 inhibitors,

	PD-1 inhibitors have a higher incidence of pneumonia in all grades (3.6% vs. 1.3%), and a higher incidence of severe pneumonia (1.1% vs. 0.4%) .
Immune-related rheumatism/musculoskeletal system toxicity	The most common is oligoarthritis or polyarthritis, and may persist after the treatment is terminated. It has been reported that about 15% of patients receiving ICI treatment experienced arthralgia, but the onset of inflammatory arthritis (usually below Grade 2) has not been systematically reported.
Immune-related toxicity (rare)	
Immune-related cardiovascular toxicity	Myocarditis, pericarditis, and cardiac insufficiency caused by ICI are rare. The true incidence is unknown, and the estimated incidence is less than 1%. Immune-related cardiotoxicity may manifest as non-specific symptoms in the early stage, such as fatigue and weakness. Within a few months, patients may present with symptoms such as chest pain, shortness of breath, edema of the lungs or lower extremities, palpitations, arrhythmia, heart failure, or new heart block. Other symptoms may include muscle pain or syncope. ICIs cannot be rejected solely based on potential cardiotoxicity (including patients with known cardiac complications), but all must be vigilant.
Immune-related nephrotoxicity	The incidence of nephrotoxicity when receiving ICI monotherapy is 2%, which may be related to pathological examinations just beginning to describe relevant characteristics and reports.
Immune-related ocular toxicity	Such toxicity mainly manifests as uveitis (more common in the anterior part than in the posterior part or all), with an incidence of <1%.
Immune-related nervous system toxicity	The overall incidence is 6%. Most of the toxicity is mild and manifests as non-specific symptoms, such as headache; the incidence of Grade 3 and above irAEs is <1%.
Immune-related blood system toxicity	Such toxicity is very rare. There have been cases of irAEs in the blood system after ICI treatment, such as hemolytic anemia, red cell aplasia, neutropenia, thrombocytopenia, myelodysplasia and hemophilia A.
Infusion reactions	
Infusion reactions	It is reported that 25% of patients treated with avelumab have experienced infusion reactions (all grades) (prophylactic administration of acetaminophen and antihistamines before the administration of ICIs is recommended). The proportion of patients receiving other approved ICI treatments who experience infusion reactions (all grades) is less than 10%. The proportion of patients with severe/life-threatening infusion reactions is less than 2%.

For the diagnosis, treatment and follow-up of immune-related toxicity, please refer to the *ASCO Clinical Practice Guidelines for Management of Immunotherapy-Related Toxicities (2018)* [16]. Please refer to the attachment. Please refer to Section 5.7 for the treatment actions taken for GB226.

8.2 Laboratory Abnormal

8.2.1 Laboratory tests

The results of laboratory tests/vital signs need to be recorded in the eCRF. Abnormal laboratory findings that meet the SAE criteria are reported as SAEs and also required to be recorded as AEs in the CRF.

Clinically significant abnormal laboratory tests/vital signs found during the treatment will be recorded in the eCRF as a diagnosis record if they meet at least one of the following criteria.

- Accompanied by clinical symptoms
- Leading to study medication change (e.g. dose adjustment, suspension or permanent discontinuation, etc.)
- Requiring changes in the concomitant treatments (e.g., adding, suspending, stopping or changing concomitant medications/treatments)
- Leading to interruption of the investigational drug
- The investigator insists on reporting it as an adverse event: If an abnormal laboratory test/vital sign is related to clinical symptoms/signs, the corresponding clinical symptoms/signs should be reported as an adverse event.

8.2.2 Follow-up visit for abnormal laboratory findings

Any abnormal laboratory findings that are clinically significant and inexplicable should be tested repeatedly and followed up to baseline levels, or should be reasonably explained and recorded in the eCRF.

8.2.3 Progressive disease/condition

The natural progression, deterioration or recurrence of the disease and/or condition under study will be recorded as part of the efficacy evaluation and should not be recorded as an AE/SAE.

8.3 Handling of Adverse Events

8.3.1 Reporting of adverse events and time limit

During the trial, the investigator needs to closely monitor the clinical and laboratory data of each subject's adverse events. The investigator needs to evaluate and record any adverse event in detail, including the date of onset, symptoms, severity, outcome, duration, and outcomes, the relationship between the adverse event and the investigational drug, the diagnosis of an adverse event and the actions taken. For serious adverse events that are unlikely related to the investigational drug, the investigator should provide other reasons for the adverse event.

For adverse events considered to have intermittent attacks, each attack of the adverse event must be of similar nature and severity. Regardless of whether from the medical history, or from the observations of the investigator, or spontaneously reported by the subject, all adverse events need to be recorded.

All adverse events will be followed up until recovery and return to baseline level, or the investigator believes that the condition is stable, or the subject is lost to follow-up, or the subject withdraws the informed consent.

All adverse events and serious adverse events will be collected from the signing of the ICF to 90 days after the end of the last dose of investigational drug GB226. Adverse events and serious

adverse events related to the investigational drug should still be collected 90 days after the end of the last GB226 administration.

8.3.2 Reporting of serious adverse events and time limit (immediate reporting)

The investigator should give timely rescue and treatment for any serious adverse events that occur during the trial regardless of whether they are related to the investigational drug or not, and report to the drug regulatory authority of the relevant provinces, autonomous regions, and municipalities under the Central Government and the National Medical Products Administration within 24 hours of awareness. The investigator should also report to the hospital's Ethics Committee in time according to the requirements of the study site and notify the sponsor (fax: 021-6169 0706) or the third-party service provider designated by the sponsor. For SAEs, the description of symptoms, severity, onset time, time of treatment, actions taken, time and method of follow-up, and outcome (using the onset date and end date of the SAE severity as the start date and end date of the SAE) should be recorded in detail.

The investigator must provide causality assessment when reporting SAEs.

If a AE cannot be determined to be a SAE by the investigator, all will be regarded as SAEs before the nature can be determined.

For all serious adverse events (including any SAE that occur in the development phase after the end of the trial and within 90 days of the last dose and drug-related SAEs that occur 90 days after the last dose), the investigator needs to follow them up until there is a clear outcome, and ensure that all problems are resolved. Detailed follow-up information should be provided (e.g. after the end of study, whether special treatment is needed, whether hospitalization required). For each serious adverse event, at least the following materials should be provided to the sponsor or the designated third-party service provider within 24 hours:

- Study protocol No.
- Site No.
- Name of investigator
- Subject No.
- Name of serious adverse event
- Date of occurrence
- Causality evaluation
- Criteria of severity
- Date of and the reason for death (if applicable)

After the following supplementary materials are obtained, they must be provided to the sponsor or the designated third-party service provider immediately:

- Severity of event

- Outcome (if it has been resolved, fill in the date of resolution)
- Withdrawal statement (yes or no)
- Simultaneous treatment (indicate the treatment for adverse events)
- Date of birth and gender
- Other current diseases
- Relevant medical history

8.3.3 Reporting of non-serious adverse events of special interest

Infusion reactions:

If adverse events occur during the infusion of the investigational drug or within 1 hour after the end of the infusion, these events may be related to the infusion.

Overdose:

Overdose is defined as a dose 20% or more of the actual dose. If an overdose occurs, the drug should be stopped immediately and the subject should be closely monitored, regardless of whether there are any symptoms related to the overdose. All symptoms related to drug overdose should be reported as adverse events.

Grade 3 or higher infusion reactions and drug overdose should be notified to the sponsor or the designated third-party service provider within 24 hours of awareness. For the specific process, see the trial safety management plan.

8.3.4 Pregnancy

If a subject or a subject's spouse becomes pregnant during the trial, the investigator must be notified immediately and the investigational drug must be stopped. If a subject becomes pregnant within 6 months after the end of treatment with the investigational drug, the subject should also notify the investigator. The investigator should report to the sponsor or the designated third-party service provider within 24 hours of awareness. The investigator should discuss with the subject the risks of continuing pregnancy and possible effects on the fetus. Pregnancy events should be followed up until the termination of pregnancy or 3 months after the birth of the fetus.

8.3.5 Unexpected adverse event

Unexpected adverse events refer to adverse medical events related to the study drug that occur during the trial, and are not clearly stated in the clinical study protocol, informed consent form, or Investigator's Brochure. Unexpected adverse events are determined by the sponsor and/or designated third-party service provider based on the study protocol, informed consent form, and reference safety information (RSI) contained in the Investigator's Brochure. After unexpected adverse events are confirmed, substantial modifications to the clinical study protocol or informed consent process/documents will be considered, or other corrective actions will be taken to protect the safety and rights and interests of the subjects.

9 DATA MANAGEMENT AND STATISTICAL METHOD

9.1 Data Management

This study uses RAVE® Electronic Data Capture (EDC) system to collect data. Data management plan: The plan is written by data manager (DM) as a guiding document for the whole data management process, and all data management processes should be operated according to the time, content and method defined therein.

Design of eCRF: It is required to, according to requirements in the protocol, design the data collection form, define the study procedures and data form name as well as data items collected therein, and develop the corresponding data completion guidelines, which will be finalized after reviewed by the sponsor for completion and use by study site.

Database establishment and testing: The design of the eCRF complies with the requirements of FDA 21 CFR Part 11, and complies with the provisions of the Good Clinical Practice (ICH GCP) and the Good Clinical Practice (CFDA, 2003) on data collection. The database is tested by DM in the following aspects: page design, setting of the visit period, order of entry forms and order of each data points during the visit, accuracy of different user browsing permission, etc.

Data verification and testing: Data verification includes computerized program verification and manual verification. Computer program verification should be integrated in the electronic database, and data questions should be raised in real time. During the trial, the DM should perform manual verification on the data points that are not covered by the electronic database program. The investigator should answer data queries in a timely manner, and all relevant processes for data queries should be traceable in the database. The logical verification test is performed by DM based on the data verification plan. The EDC system is tested whether or not to correctly execute triggering and closing of doubt prompts as pre-designed. Relevant documents are generated and saved during the test.

Data entry: The investigator needs to collect subject data according to requirements in GCP and study protocol, and fill in the eCRF, which is not used as the original records, according to the guidelines in an accurate, timely, compete and standard manner.

On-site source data verification (SDV): The CRA logged onto the EDC at each study site to check consistency of eCRF data with source data and could report problems online at any time if there were.

Questions and answers: The investigator can answer questions online in real time, or CRC will enter the query updates or answers into EDC. DM and monitor will check and reply to the solution by the investigator and can question again if necessary until data are "clean".

External data management: External data should be transmitted and managed according to the external data transmission protocol, and the DM will check the consistency of the external data with the data in the EDC.

Medical coding: The medical history, adverse events, and non-drug treatments in this trial will be coded using the MedDRA dictionary, and concomitant medications will be coded using the WHODD.

Data locking and exporting: When all subjects complete the trial and all medical records are entered into the system and all data queries are answered, data will be locked by the DM after the principal investigator, sponsor, statistical analysts and DM review these data and confirm that the established database is correct. After all the data is locked, the DM will submit the final data set exported from the database to the statistician for statistical analysis. After the data is locked, if there is definite evidence that it is necessary to unlock, the principal investigator, the sponsor, the statistical analysts, and the DM can jointly sign the database unlock confirmation form to update the data, and all updates must be documented. After the update is completed, the database lock process needs to be executed again.

Archiving of eCRF: After the trial, the eCRF of each subject is generated in a PDF format and turned to a CD for archiving.

Data management report: After the trial, DM writes the data management report according to the actual execution of the project.

9.2 Statistical Analysis

9.2.1 Evaluation of variables

Primary efficacy endpoint:

- Overall response rate (ORR)

Secondary efficacy endpoints:

- Duration of response (DOR)
- Time to response (TTR)
- Disease control rate (DCR)
- Progression-free survival (PFS)
- Overall survival (OS)

Safety evaluation measures include:

- Adverse event
- Physical examination
- Vital signs
- Electrocardiogram
- Laboratory tests (blood routine, urine routine, stool routine, blood biochemistry, LDH, β-microglobulin, thyroid function, pregnancy test, etc.)

Immunogenicity evaluation measures include:

- Anti-GB226 antibody (ADA)

Biomarker evaluation measures include:

- Expression of programmed cell death protein ligands-1 and 2 (PD-L1/PD-L2), deficient mismatch repair genes (dMMR) and/or microsatellite instability (MSI), tumor mutation burden (TMB)
- Immune cell typing and counting include B lymphocytes [CD19+], T lymphocytes [CD3+] and their subtypes [CD4+ and CD8+ T cells] and NK cells [CD16+CD56+]
- Cytokines include interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor α (TNFα), and interferon gamma (INFγ).

9.2.2 Analysis set

Full analysis set (FAS): including all subjects who are administered with at least once investigational drug.

Safety Set (SS): Including all subjects who have received the trial medication at least once and have at least one post-dose safety assessment.

Per-protocol Set (PPS): Including all subjects in the FAS who have not used any concomitant medications that may affect the efficacy evaluation during the trial period, have complete primary evaluation measures, and have no major protocol deviations. All protocol deviations resulting in the exclusion of subjects from the PPS will be described in detail in the Statistical Analysis Plan (SAP) and completed before data lock.

9.2.3 Statistical method

The data cut-off time for primary statistical analysis is planned to be carried out after the completion of two efficacy assessments of the last subject, or in the following situations: progressive disease, start of subsequent anti-tumor treatment, death or loss to follow-up, subject withdrawal of informed consent or discontinuation of treatment, whichever occurs first (i.e., the statistical analysis data cutoff time point is no earlier than the above time point).

For statistical analyses, SAS V9.4 will be used for programming and calculations.

It is planned to combine the data of the various sites participating in this trial for analysis. Descriptive statistics will be used to analyze demographic and baseline characteristics, efficacy and safety data. For continuous variables, number, mean, standard deviation, median, minimum, and maximum will be presented. For categorical variables, the frequency and percentage will be described in lists.

Baseline is defined as the last observation data prior to the first dosing.

The detailed analysis method will be explained in the SAP.

9.2.3.1 Subject disposition

In the Full Analysis Set, the number and percentage of subjects enrolled in each site, the completion of the trial, and the reason for withdrawal are summarized. The number and percentage of subjects in each data set will be statistically analyzed.

9.2.3.2 Baseline and demographic characteristics

In the Full Analysis Set, the demographic data and baseline characteristics will be tabulated and descriptively summarized.

The related medical history and current medical history will be summarized according to the system organ class and preferred term (MedDRA).

9.2.3.3 Compliance and drug exposure analysis

The compliance with the protocol will be assessed by the number and proportion of patients with major protocol deviations (Major PD); compliance with the investigational drug will be assessed based on the relative dose intensity and the number of missed doses. The analysis will be performed in the form of lists and summaries.

The subjects' actual cumulative dose, drug exposure time, dose intensity (calculation method: dose intensity = actual cumulative dose/drug exposure time) and relative dose intensity (calculation method: relative dose intensity = dose intensity/planned dose intensity × 100%) will be calculated, and summarized with descriptive statistics. The relative dose intensity categories will be specified in the SAP. The number and proportion of patients in each category will be given.

9.2.3.4 Efficacy analysis

The efficacy variables will be analyzed based on the Full Analysis Set (FAS) and the Per-protocol Set (PPS), respectively. The FAS analysis result will be used as the main basis, and the PPS analysis result as the supporting basis; the IRC's efficacy evaluation result will be used as the main basis, and the investigator's efficacy evaluation result as the supporting basis; the efficacy evaluation result according to the 2014 Lugano criteria will be used as the main basis, and the efficacy evaluation result according to the modified criteria for immunotherapy as the supporting basis.

Primary efficacy variable:

The primary efficacy variable is the overall response rate (ORR) of GB226 in the treatment of patients with relapsed or refractory primary mediastinal large B-cell lymphoma. ORR is defined as the proportion of subjects whose best efficacy is CR and PR through imaging assessment. The first CR or PR should be confirmed at least 4 weeks later.

The primary analysis of the study is to assess the ORR (based on the IRC's evaluation result) of GB226 in patients with relapsed or refractory primary mediastinal large B-cell lymphoma, and perform the exact test of the following superiority hypothesis on the ORR at the one-sided $\alpha = 0.025$:

H0: ORR ≤25% vs. Ha: ORR＞25%;

The Clopper-pearson method will be used to give an ORR estimate and a 95% confidence interval. If the lower limit of the interval is greater than 25%, the trial is considered to be successful, and the efficacy of GB226 in patients with relapsed or refractory PMBCL will be considered as clinically significant.

Supporting analysis:

All the above analyses will be repeated on the PPS. The above analyses will be performed based on the investigator's assessment of the tumor and progressive disease.

Secondary efficacy variables:

The duration of response (DOR), time to response (TTR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) will be analyzed by using descriptive statistical methods. The Clopper-pearson method will be used to estimate ORR and DCR, and provide the corresponding 95% confidence intervals. The Kaplan-Meier method will be used to analyze DOR, TTR, PFS and OS, and provide the medians and 95% confidence intervals.

9.2.3.5 Safety analysis

The analysis of safety evaluation endpoints will be performed in the safety set.

Adverse event

Adverse events will be coded using the Chinese version of the Medical Dictionary for Regulatory Activities (MedDRA), and TEAEs will be summarized according to system organ class (SOC), preferred term (PT) and CTCAE classification. The number of subjects, number of events and incidence of adverse events of all subjects and adverse events related to the study drug will be statistically analyzed. The incidence of AEs is recorded as 1 case if multiple AEs occur in one patient or the same AE occurs frequently in one patient. The listings of adverse events will be presented. The AEs that occur during the screening period and before medication will only be tabulated.

Laboratory tests

For each laboratory test, descriptive summary analyses will be performed on each parameter at each planned time point, and all completed test items will be summarized in the form of a cross table before and after treatment. Subjects' test items which are normal before treatment and abnormal after treatment, and items which are abnormal before treatment and still abnormal after treatment will be listed, and a list of laboratory test results of all subjects will be provided.

Vital signs

The number and percentage of patients with abnormal vital signs will be summarized in the form of a cross table before and after treatment. Subjects' test items which are normal before treatment and abnormal after treatment, and items which are abnormal before treatment and still abnormal after treatment will be listed, and a list of vital signs of all subjects will be provided.

Electrocardiogram (ECG)

The number and percentage of patients with abnormal ECGs will be summarized in the form of a cross table before and after treatment. Subjects' ECG assessments which are normal before treatment and abnormal after treatment, and which are abnormal before treatment and still abnormal after treatment will be listed, and a list of ECG assessments of all subjects will be provided.

Immunogenicity analysis

The number and percentage of patients with anti-GB226 antibodies (ADA) will be summarized, and a graph of the changes in the patient's GB226 antibody levels over time will be plotted.

9.2.3.6 Biomarkers

Subgroup analyses will be performed on the efficacy variables, and the tumor biomarkers and immune cell typing and counting results in each group will be described If necessary, the correlation between tumor markers & immune cell typing and counting and efficacy parameters may be explored by using graphic methods.

9.2.3.7 Concomitant medication

The WHODD will be used to code and summarize concomitant medications and important non-drug treatments before and after treatment.

9.2.3.8 Interim analysis

No formal interim analysis is planned for this study.

9.2.4 Sample size calculation

The primary endpoint of this study is the overall response rate (ORR) of the study treatment of relapsed or refractory PMBCL. For patients with relapsed or refractory PMBCL who have undergone autologous stem cell transplantation or who have failed to respond to at least second-line or above systemic treatment, ORR >25% is considered to have clinically significant anti-tumor activity. It is expected that the ORR of GB226 in this population can reach 45%, and the following efficacy hypothesis test is performed at the level of one-sided $\alpha = 0.025$: H_0: ORR $\leq$ 25% vs. H_a: ORR > 25%, 42 subjects can provide a > 80% power to detect the efficacy; when the observed ORR is 40%, 45% or 50%, the two-sided 95% exact confidence interval given by 42 subjects is shown as following table. Given a dropout rate of about 20%, the study plans to enroll 53 patients with relapsed or refractory PMBCL.

ORR observation value	Two-sided 95% confidence interval
40%	[25.2%，56.2%]
45%	[29.6%，61.1%]
50%	[34.2%，64.8%]

10 PROTOCOL VIOLATION

The investigator should implement the study in strict accordance with the protocol. Any subject whose study medication deviates from the protocol or who does not meet the important inclusion/exclusion criteria for the study may be excluded from a certain study analysis set and may affect the study results. Any protocol deviation or violation, if found, should be reported to the sponsor or the relevant responsible person of the CRO in accordance with the time limit and process specified by the study. The investigator should report any protocol deviation or violation that may have an important impact on the safety of subjects or the suitability of participating in this study to the medical monitors of this study in time, and discuss with them and obtain medical advice therefrom. In addition, the investigator and his/her study team must abide by the ICH-GCP principles and all applicable domestic laws and regulations in their operations.

11 ETHICS AND REGULATIONS

11.1 Good Clinical Practice

The implementation of the study should comply with the *Good Clinical Practice* (ICH GCP) of the *Declaration of Helsinki*, and applicable laws and regulations, so as to protect subjects as much as possible.

11.2 Informed Consent and Inform Consent Form

Before the start of the trial, the investigator should explain the nature, objectives, potential risks and benefits of the trial to the subjects, and should also inform the subjects that they can freely withdraw from the trial at any time. The subjects should be given an opportunity to ask questions and time for consideration. If neither the subject nor his/her legal representative can read the informed consent form, a witness should be present during the informed consent process. After the subject and his/her legal representative have orally consented to the subject's participation in the study, the witness should sign the informed consent form and ensure that the subject and his/her legal representative are fully informed and understand these contents.

Before the start of the trial, the informed consent form signed and dated by each subject must be obtained. The original copy should be kept by the investigator as part of the trial records, and a copy of the signature page will be kept by the subject. It must be explained to subjects that the sponsor's authorized personnel may consult their relevant medical records.

If safety results make risk/benefit evaluation change significantly, the informed consent form should be audited and changed if necessary. All patients (patients who have received treatment) should be informed about the updated information. The study can continue after all patients signed a new informed consent form.

11.3 Protection of Subjects' Privacy

The informed consent form informs subjects that the trial will comply with data protection and privacy regulations. Subjects should also authorize the investigator or other relevant personnel who need to know this information to collect, use, and publish their data. The informed consent will also inform subjects that the trial data will be stored in a computer database, which will be kept confidential in accordance with China's corresponding laws. The data in the database can only be identified based on the random number/trial number/initials (the first letters of their name in Pinyin). The informed consent form will also inform subjects that in order to verify the data, representatives authorized by the sponsor, national regulatory agencies, ethics committees and other relevant staff can directly access some hospital or medical records related to this trial.

The investigator must ensure that the subject's privacy is not disclosed to unauthorized third parties. eCRFs and other documents submitted to the sponsor will not contain subject name and will be identified only by an identification code. The investigator may maintain an enrollment form that includes subject identification code, name, and address. The informed consent form and other documents should be strictly confidential and should not be submitted to the sponsor.

11.4 Protocol Amendment

Without the consent of both the principal investigator and the sponsor, the trial protocol and process cannot be changed. If the trial protocol must be modified, the revised protocol must be submitted to IEC/IRB for approval. Before obtaining IEC/IRB approval, the investigator should still follow the original trial protocol, unless the revised content of the protocol can immediately eliminate the potential harms to the subjects, or the revised content of the protocol only involves changes in trial management (e.g., telephone number changes, etc.).

11.5 Independent Ethics Committee/Institutional Review Board

The clinical trial protocol and its amendments, the Investigator's Brochure, informed consent form, subject information (e.g., advertisements for recruiting subjects) and other necessary documents should be submitted to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) for approval.

The approval of IEC/IRB must be obtained before the trial starts. The EC approval letter should contain review or approval opinions as well as name, gender and occupation of EC members. The approval of the Ethics Committee should also indicate the approved trial number, trial title, document content (version number/version date), and the date of signature and approval by the members of the Ethics Committee.

Any revision of the protocol should be approved or filed by the IEC/IRB formally.

All serious adverse event will be reported to relevant ethics committee and regulatory authorities according to regulations.

During the study, the investigator should rapidly report to the IEC/IRB if protocol deviation may increase risks to subjects.

11.6 End and Termination of the Trial

The end of the trial is defined as that the last subject withdraws the informed consent, discontinues the treatment or withdraws from the trial, is lost to follow-up or dies, the treatment has been completed for 2 years, or the study ends early, whichever occurs first.

Termination of study: The Sponsor has the right to terminate the study. Both parties must arrange related procedures after review and negotiation. After deciding to terminate the trial, the sponsor and the investigator must ensure that they fully consider protecting the interests of subjects.

After the trial is terminated, the sponsor should submit a written notice to the regulatory authority; the investigator or sponsor should submit a written notice to the IEC/IRB.

After the trial is terminated, the investigator should return, destroy or save the trial data in accordance with the requirements of the sponsor.

11.7 Retention of Trial Data

The investigator should fully and accurately record study processes and make the study data verifiable. The documents can be divided into two categories: investigator's documents and subjects' original data.

Investigator's documents include study protocol and revisions, CRFs and data query forms, approval certificates and correspondences with IEC/IRB and regulatory authorities, ICF sample, drug records, investigators' CV and authorization list, other necessary documents and letters.

Subjects' original documents (key efficacy/safety data that need to be recorded should be defined in advance) include patients' hospitalization/outpatient record, medical orders from physicians and nurses, appointed visit date, original laboratory results, ECG, EEG, imaging data, pathological report and special evaluation report, signed informed consent form, consultation record, subject identification code form, and screening and enrollment forms.

The above-mentioned trial data should be kept until 5 years after the investigational drug is marketed in the last country or 5 years after the investigational drug development is officially terminated. However, due to differences in international regulations or national regulations, the sponsor may require the trial data to be kept for a longer period of time. For example, the EU regulations require preservation for at least 15 years.

If the investigator is willing to transfer these study documents to a third party or another place, the sponsor should be notified in advance.

If the investigator cannot guarantee that these documents can be kept intact at study sites, the investigator and the sponsor can keep the documents in other place, and the documents should be sealed, so that the investigator can take back the documents when regulatory authorities audit. If the documents are still used, their copies can be kept in another place.

12 MONITORING AND AUDIT

The sponsor will conduct monitoring and audits in accordance with the requirements of ICH GCP to ensure that trial data and records are available onsite.

12.1 Trial Monitoring and Source Data Verification

The clinical monitors assigned by the sponsor will regularly conduct on-site monitoring visits to the trial hospital to ensure that all the contents of the trial protocol are strictly followed and guarantee the correctness and completeness of the filling of trial data. In addition to monitoring visits, regular communication (by email, telephone, fax, etc.) will be conducted to ensure that all trial activities meet the requirements of the protocol and regulations.

All observation results in the clinical trial should be verified to ensure that the data are reliable and the conclusions of clinical trials are obtained based on the original data. At the stages of clinical trial and data processing, corresponding data management measures must be taken.

12.2 On-site Audit/Inspection

The investigator should ensure that when the sponsor, IEC/IRB or the drug regulatory authority conducts audits/inspections of the study site, they can directly access the original documents, eCRF and other trial documents in the trial. The data in the eCRF should be directly derived from the original materials, and the investigator should offer vigorous support and cooperation. The purpose of the audit or inspection is to systematically and independently check the behaviors and documents related to the trial, to confirm that these behaviors have been implemented, the data has been recorded and analyzed, and the trial protocol, ICH GCP guidelines and regulatory requirements have been complied with.

When learning that the regulatory department requires inspection of the site, the investigator should immediately contact the sponsor.

13 RECORDING AND USE OF TRIAL RESULTS

13.1 Recording of Trial Results

The investigator (or his/her authorized representative) should collect data in accordance with the requirements of the protocol and record it in the eCRF. If the investigator authorizes others to fill in the eCRF, he/she should provide the sponsor with the name, position, signature and initials of the authorized representatives.

After obtaining the trial information of a subject, the investigator should fill in the eCRF as soon as possible. The reason for any missing data should be explained.

The information of subjects who have failed the screening should also be recorded in the eCRF and the original materials.

The investigator should review the completed eCRF and sign for confirmation.

The sponsor keeps the original eCRF, and the investigator keeps the copy.

13.2 Use of Trial Results

All information about the investigational drug that is provided by the sponsor and has not been published, such as the indications, dosage form, production process and other test data of the investigational drug, is the sponsor's independent intellectual property rights and confidential information. The investigator should agree that the published information will only be used to carry out this trial, and will not be used for other purposes without the written consent of the sponsor. The trial results belong to the sponsor.

The investigator should agree that the trial results will be used for domestic and foreign drug registration and publication. The name, address, qualifications and responsibilities of the investigator should be notified to the drug regulatory authority.

The sponsor is responsible for writing the final clinical trial report, and the principal investigator should declare that the trial report accurately describes the trial process and trial results. The trial results should be submitted to the drug regulatory authority or IEC/IRB.

All the materials and information provided by the sponsor, and all the materials and information generated in this trial, should be the sponsor's intellectual property rights. The investigator has the right to publish the results of this trial, provided that a complete copy is sent to the sponsor at least 45 days before the article or abstract is submitted. The sponsor has the right to review and approve the article to be published, including oral presentations or summaries using the data of this trial. When necessary, the investigator should comply with the sponsor's confidentiality requirements for such materials and agree to keep them for 90 additional days, so that the sponsor has time to apply for patents or other intellectual property protection.

Before the start of the trial, the sponsor and the investigator should reach an agreement on the method and time of publication of the article.

14 REFERENCES

[1] Ranjana H. Advani, MD. Advances in the Management of Primary Mediastinal Large B-Cell Lymphoma. Clinical Advances in Hematology & Oncology Volume 16, Issue 1 January 2018; 33-34.

[2] Johnson P, Delabie J, Rodig S, et al. Primary Mediastinal Large B-Cell Lymphoma[M]// Rare Lymphomas. Springer Berlin Heidelberg, 2014:877-88.

[3] G Todeschini, S Secchi, E Morra, et al. Primary mediastinal large B-cell lymphoma (PMLBCL): long-term results from a retrospective multicentre Italian experience in 138 patients treated with CHOP or MACOP-B|[sol]|VACOP-B[J]. British Journal of Cancer, 2004, 90(2):372-376.

[4] PL Zinzani, M Martelli, M Bertini, et al. Induction chemotherapy strategies for primary mediastinal large B-cell lymphoma with sclerosis: a retrospective multinational study on 426 previously untreated patients. [J]. Haematologica, 2002, 87(12):1258.

[5] Zinzani P L, Piccaluga P P. Primary mediastinal DLBCL: evolving biologic understanding and therapeutic strategies. [J]. Current Oncology Reports, 2011, 13(5):407-415.

[6] National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: B-cell Lymphomas, V. 5, 2017.

[7] Gharwan H, Lai C, Grant C, et al. Female fertility following dose-adjusted EPOCH-R chemotherapy in primary mediastinal B-cell lymphomas[J]. Leukemia & Lymphoma, 2016, 57(7):1616-1624.

[8] Dunleavy K, Pittaluga S, Maeda L S, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma.[J]. N Engl J Med, 2013, 368(15):1408-1416.

[9] Grigoropoulos N F, Nagumantree S, Hodson A, et al. Dose-adjusted R-EPOCH for the treatment of primary mediastinal B-cell lymphoma: the West Anglia experience[C]// Scientific Meeting of the British-Society-For-Haematology. 2014:55-56.

[10] Dunleavy K, Steidl C. Emerging Biological Insights and Novel Treatment Strategies in Primary Mediastinal Large B-Cell Lymphoma. [J]. Seminars in Hematology, 2015, 52(2):119-125.

[11] Shi M, Roemer M G, Chapuy B, et al. Expression of programmed cell death 1 ligand 2 (PD-L2) is a distinguishing feature of primary mediastinal (thymic) large B-cell lymphoma and associated with PDCD1LG2 copy gain.[J]. American Journal of Surgical Pathology, 2014, 38(12):1715-1723.

[12] Tanaka Y, Maeshima A M, Nomoto J, et al. Expression pattern of PD-L1 and PD-L2 in classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, and gray zone lymphoma[J]. European Journal of Haematology, 2018.

[13] Xu-Monette Z Y, Zhou J, Young K H. PD-1 expression and clinical PD-1 blockade in B-cell lymphomas[J]. Blood, 2017, 131(1): blood-2017-07-740993.

[14] Pier L Z, Vincent R, Craig H. M, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Blood. [J].2017, 130(3):267-270.

[15] FDA label of Keytruda. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125514s030lbl. pdf

[16] Brahmer J R, Lacchetti C, Thompson J A. Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline Summary[J]. Journal of Oncology Practice, 2018, 36(17):JOP1800005.

[17] Bruce D. Cheson, Stephen Ansell, Larry Schwartz, et al: Refinement of the Lugano Classification lymphoma response criteria inthe era of immunomodulatory therapy. Blood. 2016, 128(21):2489-2496.

[18] Bruce D. Cheson, Beate Pfistner, Malik E. Juweid, et al: Revised Response Criteria for Malignant Lymphoma. J Clin Oncol 2007, 25: 579-586.

[19] Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, et al Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol 32:3059-306, 2014.

15 APPENDICES

15.1 Appendix A: Treatment of Infusion Reactions and Anaphylactic Shock

I. Treatment of Infusion Reactions

Infusion reactions that occur in clinical use of GB226 mostly occur during the first infusion or within 1 hour after the infusion, and mainly manifest as fever, hypothermia, chills, dizziness, urticaria, dyspnea, hypotension and other symptoms. Once the above infusion reactions occur during the infusion process, stop the infusion as soon as possible, inhale oxygen, and use conventional antipyretic analgesics (e.g., acetaminophen, etc.), anti-allergic drugs (e.g., diphenhydramine, etc.), corticosteroids and other treatments. After the symptoms are recovered, the infusion rate must be reduced during subsequent infusions. If the patient experiences serious infusion reactions, such as hypersensitivity, allergic reactions, and angioedema, the investigational drug treatment should be stopped, and emergency medical treatment should be implemented in accordance with clinical diagnosis and treatment routines.

II. Treatment of Anaphylactic Shock

1. Clinical manifestations

After exposure to allergens, lightning attacks occur, and serious reactions often occur within 15 minutes. A small number of patients can experience reactions after 30 minutes or even several hours, which are called “delayed reactions”.

Early clinical manifestations are mainly general malaise, numbness of lips, tongue and feet, itchy throat, dizziness and giddiness, palpitation, chest tightness, nausea, vomiting, and irritability. The patient immediately presents with collapse, profuse sweating, pale complexion, cyanosis of the lips, throat edema, polypnea, and cold limbs, as well as diffuse skin flushing and rash, hand and foot edema. Some patients feel dying and horror. In severe cases, there are coma, gatism, myosis or mydriasis, confusion, weakened heart sounds, rapid heart rate, pulselessness, blood pressure drop, and even undetectable blood pressure.

2. Principle of handling

Quick treatment is very important for anaphylactic shock. Immediately stop allergenic drugs, measure the blood pressure, palpate the pulse, observe the breathing, and immediately inject epinephrine, glucocorticoids, hypertensive drugs, desensitizers.

(1) General treatment measures:

1) Get rid of allergens immediately, and remove the cause and incentives.

2) Take the shock position: raise the head and trunk by 20°-30°, and raise the lower limbs by 15°-20° to increase the return blood volume and alleviate dyspnea.

3) Keep the respiratory tract unobstructed.

4) Oxygen inhalation.

(2) First aid and treatment

1) Epinephrine: When anaphylactic shock is discovered, immediately inject epinephrine. Adults can be given 0.5-1 mg by intramuscular injection, or an intramuscular injection at the original injection site can be given to reduce the absorption of sensitizing drugs, and exert an anti-allergic effect. The effect of epinephrine is short-lived. If it does not work after the first injection, consider repeating the injection within 1 to 5 minutes.
2) Adrenocortical hormone: Such drug is effective in combating allergies and increasing blood pressure. Dexamethasone 10-20 mg can be administered each time by intramuscular injection or intervenous bolus injection, or methylprednisolone 100-300 mg can be injected intravenously.
3) Hypertensive drugs: Commonly used are aramine 10-20 mg and dopamine 20-40 mg intravenously or intramuscularly. If the blood pressure still does not rise after the above treatments, intravenously inject norepinephrine 1 mg diluted with 10 ml, or intravenously infuse norepinephrine 2-4 mg plus 5% glucose saline 250 ml, but do not administer by intramuscular injection or subcutaneous injection to avoid local ischemia and necrosis.
4) Desensitization drugs: Use promethazine (phenazine) 25-50 mg intramuscularly or intravenously or plus 5-10% glucose solution 250-500 ml intravenously, or chlorpheniramine 10-20 mg intramuscularly or added to infusion for intravenous infusion, or diphenhydramine 25-50 mg intramuscularly. Or administer 10% calcium gluconate 10-20 ml plus 5-10% glucose solution slowly intravenously or intravenously, and if necessary, repeat the administration after 30 minutes.
5) Oxygen inhalation: Oxygen inhalation is very necessary, especially in severe cases. It has a good effect in correcting hypoxemia and improving respiratory failure.
6) Infusion problems: Due to the expansion of peripheral vasculature and insufficient blood volume, the increase in the dosage and rate of infusion will help improve the systemic and local circulation, and promote the excretion of allergic substances. Generally, start with 5% dextrose saline 1000 ml. If the patient has manifestations of pulmonary edema, slow down the infusion rate and switch to sugar water to avoid aggravating the disease, or administer dextran or hydroxyethyl starch by rapid infusion, and replenish according to the actual situation.
7) After the shock is improved, if the blood pressure is still fluctuating, maintain the vasoactive drugs by continuous intravenous infusion; if the patient has angioedema, wheal and other skin damage, oral prednisone 20-30 mg per day can be administered in divided doses, as well as antihistamines, such as astemizole 10 mg qd or bid, and chlorpheniramine 4 mg po tid. Supplement vitamin C, and closely observe the patient for 24 hours to prevent the recurrence of anaphylactic shock.

The condition of allergic physique is very serious, and it is very important to strengthen prevention. Notes:

1) Avoidance of drug abuse: It is emphasized that physicians should strictly master the

principles of drug use, use drugs according to the indications, and avoid drug abuse, which is an important measure to prevent drug-induced anaphylactic shock.

2) Inquiry about the history of allergies: Before a drug is used, the patient must be inquired about the history of allergies, such as urticaria, asthma, eczema, drug eruption, and allergic rhinitis. If the patient has a history of allergies, all should be vigilant when using drugs. If the patient has had an allergic reaction to a certain drug, it is prohibited to use the drug again.

3) Skin allergy test.

4) Raise vigilance and strengthen observation: Many drugs have the possibility of causing allergic reactions. Therefore, patients who have been injected with drugs should stay in the observation room for 20-30 minutes to prevent accidents. Particular attention should be paid to patients with a history of allergies.

5) Prevention of a second shock: Some patients have experienced anaphylactic shock before, but failed to pay much attention to it. As a result, a small number of patients may experience a second shock or even die. Therefore, the name of the drug that causes the disease must be identified and indicated in the most prominent place on the medical record card. And tell the patient and his/her family members, or distribute an anaphylactic shock registration card, and ask the patient to hold the card when seeing a doctor in the future for the doctor’s reference.

15.2 Appendix B: Revised Lugano Response Criteria in 2014

	Lesion area	PET-CT-based response (imaging response)	CT-based response (metabolic response)
CR	Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS; Note: Waldeyers ring and extranodal high metabolic uptake organs such as the spleen or bone marrow stimulated by G-CSF may have a metabolism higher than the mediastinal/liver blood pool. In this case, the CR should be compared with the background level.	Target lesion (lymph node) long diameter (Ldi) ≤ 1.5cm
			No extranodal lesion
	Non-measurable lesion	NA	Disappeared
	Organ enlargement	NA	Regress to normal
	New lesions	None	None
	bone marrow	No evidence of FDG-sensitive disease in bone marrow	Normal by morphology; if indeterminate, IHC negative
PR	Lymph nodes and extralymphatic sites	5PS score of 4-5 with reduced uptake compared with baseline and residual mass(es) of any size.	≥50% decrease in SPD, the total of PPD of up to 6 target lesions (Ldi×short diameter perpendicular to Ldi)
		At interim assessment, the above conditions indicate that the treatment is effective	When the lesion is too small to measure: 5 mm×5 mm
		At end of treatment, the above conditions indicate residual disease	When the lesion disappears: 0 mm×0 mm
	Non-measurable lesion	NA	Disappeared/normal, residual lesions/lesions not increased
	Organ enlargement	NA	The long diameter of the spleen is decreased by >50% of the extent of its prior increase in long diameter; the normal size of the spleen is often defaulted to be 13 cm. If the original length is 15 cm, the long diameter to qualify PR should be less than 14 cm.
	New lesions	None	None
	bone marrow	Residual uptake is higher than normal bone marrow tissue but lower than baseline; if there are	NA

		persistent nodular local abnormal changes in bone marrow, a MRI or biopsy or interim analysis is required for further diagnosis	
SD	Target lesions (lymph nodes/nodular masses, extranodal lesions)	No metabolism response: 5PS score of 4-5 at interim/at end of treatment with no significant change in metabolism from baseline	<50% increase in SPD of up to 6 target lesions, no evidence of PD
	Non-measurable lesion	NA	PD criteria are not met
	Organ enlargement	NA	PD criteria are not met
	New lesions	None	None
	bone marrow	Same as baseline	NA
PD	Individual target lesions (lymph nodes/nodular masses, extranodal lesions)	5PS score of 4-5 with an increase in uptake from baseline and (or) new increased uptake at interim/at end of treatment	Can be diagnosed if at least 1 target lesion progresses. The lymph nodes/extranodal lesions should meet the following requirements: Ldi>1.5cm ≥50% increase in PPD (compared with the smallest state) Increase in Ldi or Sdi from the smallest state: 0.5 cm (for lesions ≤ 2 cm) or 1.0 cm (for lesions >2 cm)
			The long diameter of the spleen must increase by >50% of the extent of its prior increase in long diameter; the normal size of the spleen is often defaulted to be 13 cm. If the original length is 15 cm, the long diameter to qualify PD must be > 16 cm. If there is no splenomegaly at baseline, the long diameter should be increased by at least 2 cm from the baseline; New or recurrent splenomegaly
	Non-measurable lesion	None	Clear progression of new-onset or existing non-measurable lesions
	New lesions		Regrowth of previously resolved lesions

		New high-metabolic foci related to lymphoma appear (exclude infection, inflammation, etc.), if the nature is not clear, a biopsy or interim assessment is required	A new node >1.5 cm in any axis
			A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
			Assessable disease of any size unequivocally attributable to lymphoma
	bone marrow	New or recurrent high metabolic uptake	New or recurrent involvement of the bone marrow

Deauville 5-point scale for response evaluation by PET:
1 point: uptake ≤ background;
2 points: uptake ≤ mediastinal blood pool;
3 points: mediastinal blood pool < lesion uptake ≤ liver blood pool;
4 points: uptake> liver blood pool (mild);
5 points: uptake > liver blood pool (significant, SUVmax > 2 times liver blood pool) or new lesions;
X points: new uptake is abnormal, which is considered unrelated to lymphoma;
*5PS score of 3: It suggests good prognosis under standard treatment in most patients, especially for patients undergoing interim assessments. However, in some clinical trials of de-escalation treatment, a score of 3 is considered as a poor treatment effect, and undertreatment needs to be avoided.

Measurable lesions:

Up to 6 significant lymph node/lymph node fusion masses, extranodal lesions, and both diameters are easy to measure;

(1) Lymph nodes: Lymph nodes need to be divided by region; if mediastinal and retroperitoneal lymph nodes are enlarged, these lesions should be included; measurable lymph nodes should have a long diameter > 1.5 cm;

(2) Non-lymph node lesions: Including solid organs (e.g., liver, spleen, kidney, lung, etc.), digestive tract, skin or palpable marked parts, measurable extranodal lesions should have a long diameter > 1.0 cm;

Non-measurable lesions:

Any significant lesions that cannot be regarded as measurable/evaluable are considered as non-measurable lesions. It includes:

(1) Any lymph node/lymph node fusion masses, extranodal lesions, that is, all parts that have not been selected as significant or measurable, or that do not meet the criteria for "measurable" but are still considered to be lesions;

(2) Considered as disease involvement but difficult to quantify, such as pleural effusion, ascites, bone metastases, pia mater involvement, abdominal mass lesions, etc.;

(3) Other undiagnosed lesions requiring imaging follow-up;

Waldeyers ring and extranodal lesions (e.g., digestive tract, liver, bone marrow): FDG uptake may be higher than the mediastinal pool for the assessment of CR, but should not be higher than the surrounding background level (for example, the metabolic activity of bone marrow is commonly increased due to chemotherapy or the application of G-CSF).

(Excerpt from Chinese Society of Clinical Oncology's (CSCO) Guidelines for the Diagnosis and Treatment of Lymphomas V1 in 2018, People's Medical Publishing House)

15.3 Appendix C: Reference Methods for Investigators to Manage Potential Immune-related Adverse Events (irAE)

By referring to the *ASCO Clinical Practice Guidelines for Management of Immunotherapy-Related Toxicities (2018)*, the following table lists the methods for the identification, diagnosis, and management of common or partly rare fatal irAEs and dose adjustments:

Potential immunity-related adverse events	**Common symptoms and signs**	**Assessment and diagnosis methods**	**Recommended management method**	**Dose adjustment**
Pneumonia	G1: Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only	Complete various examinations, including X-ray, CT and pulse oximetry; For G2 or higher, may include the following infectious workup: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity	May offer one repeat CT in 3-4 weeks; may offer a repeat spirometry/lung carbon monoxide diffusion in 3-4 weeks; may resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2	Consider suspending immunotherapy
	G2: Symptomatic; involves more than one lobe of the lung or 25-50% of lung parenchyma; medical intervention indicated; limiting instrumental activities of daily living		Prednisone 1-2 mg/kg/day and taper by 5-10 mg/week over 4-6 weeks; Empiric antibiotics; Monitor Q3 days with history and physical examination, pulse oximetry, consider CXR; No clinical improvement after 48-72 hours of prednisone, treat as G3.	Hold ICPi until resolution to ≤G1
	G3: Severe symptoms; hospitalization required; involves all lung lobes or > 50% of lung parenchyma; limiting self care activities of daily living; oxygen indicated.		Empiric antibiotics; Methylprednisolone IV 1-2 mg/kg/day; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g BID or IVIG × 5 days or cyclophosphamide; if necessary, perform bronchoscopy with BAL +/- transbronchial biopsy	Permanently discontinue immunotherapy
	G4: Life-threatening respiratory compromise; urgent intervention indicated (intubation)			

Potential immunity-related adverse events	Common symptoms and signs	Assessment and diagnosis methods	Recommended management method	Dose adjustment
Colitis	G1: Fewer than 4 bowel movements above baseline per day and no colitis symptoms.	Closely monitor: if progressive, consider stool evaluation to rule out infectious etiology.	Loperamide or diphenoxylate/atropine; Hydration	Consider suspending immunotherapy
	G2: 4-6 bowel movements above baseline per day, colitis symptoms, not interfering with activities of daily living.	Consider stool evaluation to rule out infectious etiology (it is not necessary to wait for test results before providing therapy to manage immune-related adverse events); Consider abdominal/pelvic CT with contrast; Consider GI consultation: Colonoscopy or flexible sigmoidoscopy± esophagogastroduodenoscopy (EGD) with biopsy All G2 examinations (hematology, stool examination, imaging examination, endoscopic biopsy) should be completed immediately.	Prednisone/methylprednisolone (convert to prednisone when appropriate) 1 mg/kg/day. Treat until symptoms improve to ≤G1 then taper over 4-6 weeks. No response in 2-3 days: Increase prednisone/methylprednisolone dose to 2 mg/kg/day. Consider adding infliximab	Suspend immunotherapy
	G3: More than 7 bowel movements above baseline per day. Urinary incontinence, interfering with activities of daily living (ADLs), hospitalization, other serious complications		Admit patients with dehydration or electrolyte imbalance for supportive care. Corticosteroid therapy (1-2 mg/kg/day prednisone): treat until symptoms improve to ≤G1 then taper over 4-6 weeks. If symptoms persist for 3-5 days: Continue steroids, consider adding infliximab.	Consider permanently discontinuing anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity
	G4: Seriously life-threatening.		Timely hospitalization. Closely monitor vital signs; corticosteroid therapy (1-2 mg/kg/day prednisone): treat until symptoms improve to ≤G1 then taper over 4-6 weeks. If symptoms persist for 3-5 days: Continue steroids, consider adding infliximab (5-10 mg/kg).	Permanently discontinue immunotherapy

Potential immunity-related adverse events	Common symptoms and signs	Assessment and diagnosis methods	Recommended management method	Dose adjustment
			If infliximab-refractory, consider vedolizumab.	
Hepatitis	G1: Asymptomatic (AST or ALT >ULN to 3.0 × ULN and/or total bilirubin >ULN to 1.5 × ULN)	Close monitoring of liver function parameters at G1; G2 or higher: Biopsy or radiographic evaluation to distinguish other pathogens that may cause liver damage, such as liver tumor progression, infection, and the effects of ingestion of other drugs, alcohol, and thrombotic events; Ultrasound diagnosis of liver; Exclusion of hepatitis autoimmune	G1: Closely monitor liver function for 1-2 weeks; symptomatic and supportive treatment	Continue immunotherapy
	G2: Asymptomatic (AST or ALT >3.0 to ≤5 × ULN and/or total bilirubin >1.5 to ≤ 3 × ULN)		G2: Prednisone 0.5-1 mg/kg/d or similar drugs; infliximab cannot be used for immune hepatitis; avoid the use of hepatotoxic drugs	Hold immunotherapy until recovery to G1 or prednisone ≤10 mg/d
	G3: Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis (AST or ALT 5-20 × ULN and/or total bilirubin 3-10 ULN)		G3: Prednisone 1-2mg/kg/d or similar drugs; if no improvement within 3 days, consider using mycophenolate mofetil or azathioprine; monitor liver function parameters every 1-2 days; if no improvement, refer to hepatologists, and consider liver biopsy;	Permanently discontinue immunotherapy
	G4: Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma) (AST or ALT >20 × ULN and/or total bilirubin >10 × ULN)		G4: Methylprednisone 2 mg/kg/d or similar drugs; if no improvement within 3 days, consider using mycophenolate mofetil; monitor liver function parameters every day; if still no improvement, refer to hepatologists; avoid using infliximab; intensive care if necessary.	Permanently discontinue immunotherapy
Nephritis	G1: Increase in creatinine level > 0.3 mg/dL; creatinine more than 1.5 - 2.0 × baseline level	Subjects with elevated serum creatinine should be tested for creatinine before each medication;	Consider suspending immunotherapy. Consider other alternative etiologies (intravenous contrast, medications, fluid status, etc.) and baseline renal function.	Consider suspending immunotherapy

Potential immunity-related adverse events	Common symptoms and signs	Assessment and diagnosis methods	Recommended management method	Dose adjustment
		Urinalysis is optional, unless it is necessary to rule out urinary tract infection (UTI). May need to further consider renal pathology examination; If the underlying cause of acute kidney injury (AKI) is not found, renal biopsy should be skipped, and immunosuppressive therapy should be started directly	A persistent change of <1.5 × ULN is clinically significant.	
	G2: Creatinine > 2-3 times × baseline		Consult neurology. Evaluate alternative etiologies (intravenous contrast, medications, fluid status, etc.). If other causes are ruled out, consider using 0.5-1 mg/kg/d prednisone or an equivalent dose. If worsening or no improvement: increase to 1-2 mg/kg/d prednisone or an equivalent dose; permanently discontinue immunotherapy. If improvement to ≤G1, then taper steroids over 4-6 weeks. If there is no recurrence of chronic renal insufficiency, immunotherapy can be resumed after discussing the risks and benefits with the subject.	Suspend immunotherapy
	G3: Creatinine > 3 × baseline, or > 4.0 mg/dL; hospitalization indicated			Permanently discontinue immunotherapy
	G4: Life-threatening, dialysis indicated		Consult neurology. Evaluate alternative etiologies (intravenous contrast, medications, fluid status, etc.). Corticosteroid therapy (starting dose of 1-2 mg/kg/d prednisone or an equivalent dose).	Permanently discontinue immunotherapy
Primary hypothyroidism	G1: TSH <10 mIU/L and asymptomatic	Test TSH and FT4 every 4-6 weeks as part of routine clinical monitoring	G1: Close follow-up and monitoring of TSH, fT4	Continue immunotherapy

Potential immunity-related adverse events	Common symptoms and signs	Assessment and diagnosis methods	Recommended management method	Dose adjustment
	G2: Moderate symptoms, able to Perform activities of daily living. TSH persistently >10 mIU/L	on therapy or for case detection in symptomatic patients	G2: Consider consultation with Endocrinology Department;	May suspend immunotherapy until symptoms resolve to baseline
	G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform activities of daily living		G3-4: Appropriate supplementation of hormone; Consultation with Endocrinology Department; May admit for IV therapy if signs of myxedema (bradycardia, hypothermia). Thyroid supplementation and reassessment as in G2.	May suspend immunotherapy until symptoms resolve to baseline
Hyperthyroidism	G1: No or mild symptoms	Monitor TSH, free T4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients; Consider TSH receptor antibodies if there are clinical features and suspicion of Grave's disease (e.g. ophthalmopathy); Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism	Close follow-up and monitoring of TSH, fT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism or hypothyroidism;	Continue immunotherapy
	G2: Moderate symptoms, able to perform activities of daily living		Consider endocrine consultation; Beta-blocker (e.g. atenolol or propranolol) for symptomatic relief; Supplement body fluids and supportive care; Corticosteroids are not usually required to shorten duration. For persistent hyperthyroidism (>6 weeks) or clinical suspicion of hyperthyroidism, work up for Graves' disease (TSI or TRAb) and consider thionamide (methimazole or PTU); Refer to Endocrinology for Graves disease	May suspend immunotherapy until symptoms resolve to baseline

Potential immunity-related adverse events	Common symptoms and signs	Assessment and diagnosis methods	Recommended management method	Dose adjustment
	G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform activities of daily living		G3-4: Endocrine consultation; beta-blocker (e.g. atenolol or propranolol) for symptomatic relief; For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2 mg/kg/day or equivalent tapered over 1-2 weeks. Consider also use of SSKI or thionamide (methimazole or PTU)	Suspend immunotherapy until symptoms return to baseline with appropriate treatment
Hypophysitis	G1: No or mild symptoms	Laboratory testing of endocrine parameters, including ACTH, early morning cortisol levels, TSH, FT4, and electrolytes; Consider testing LH, FSH and testosterone levels in males or estrogen, sexual function and mood changes in females; Consider brain MRI and pituitary changes in patients with multiple endocrine abnormalities or new severe headache or visual function changes	Consider suspending immunotherapy until patient is stabilized on replacement hormones; Consultation with Endocrinology Department;	Consider suspending immunotherapy
	G2: Moderate symptoms, able to perform activities of daily living			
	G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform activities of daily living		Hormonal replacement and supplementation as in G1-2; Consider the initial oral dose of prednisone 1-2 mg/kg/d or an equivalent dose for at least 1-2 weeks	Suspend immunotherapy
Rash/inflammatory dermatitis	G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	Relevant medical history and physical examination; Rule out any other etiology of the skin problem; Biopsy skin;	G1: Treat with topical emollients and/or mild-moderate potency topical corticosteroids. Counsel patients to avoid skin irritants and sun exposure.	Continue immunotherapy
	G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis.		G2: Consider initiating prednisone (or equivalent) at dosing 1 mg/kg tapering	Consider suspending immunotherapy until

Potential immunity-related adverse events	Common symptoms and signs	Assessment and diagnosis methods	Recommended management method	Dose adjustment
		Consider clinical monitoring with use of serial clinical photography; Review full list of patient medications to rule out other drug-induced cause for photosensitivity	over at 4 weeks. In addition, treat with topical emollients, oral antihistamines and medium-to-high potency topical corticosteroids.	skin AE has reverted to grade 1
	G3: As grade 2 but with failure to respond to indicated interventions for a grade 2 dermatitis		G3: Treat with topical emollients, oral antihistamines and high potency topical corticosteroids. Give 1-2 mg/kg (methyl) prednisolone tapering over at least 4 weeks	Suspend immunotherapy
	G4: Prior interventions ineffective or intolerable		G4: Systemic steroids: IV (methyl) prednisolone dosed at 1-2 mg/kg with slow tapering when the toxicity resolves. Monitor closely for progression to severe cutaneous adverse reaction. Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology	Immediately stop immunotherapy. After the skin symptoms are improved to the corticosteroid dosage reduced to prednisone ≤ 10mg, consult a dermatologist to confirm that it is appropriate to restart iPCi
Cardiotoxicity (myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis)	G1: Abnormal cardiac biomarker testing, including abnormal ECG	Perform ECG at baseline, and consider troponin examination for patients on combination immune therapies; Conduct ECG examination, creatinine protein examination, BNP examination, echocardiogram, and CXR upon signs and symptoms (if heart disease is considered);	All grades warrant workup and intervention given potential for cardiac compromise; High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms) - Admit patient, cardiology consultation - Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology	Suspend immunotherapy
	G2: Abnormal screening tests with mild symptoms			Permanently discontinue immunotherapy
	G3: Moderately abnormal testing or symptoms with mild activity			
	G4: Moderate to severe decompensation, intravenous medication or intervention required, life threatening conditions			

Potential immunity-related adverse events	Common symptoms and signs	Assessment and diagnosis methods	Recommended management method	Dose adjustment
		Other tests guided by cardiology include stress test, cardiac catheterization, and cardiac MRI	- Immediate transfer to a coronary care unit should be considered for patients with elevated troponin or conduction abnormalities. - In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or anti-thymocyte globulin	
Neurotic toxicity	Myasthenia gravis, Guillain-Barre syndrome, peripheral neuropathy, autonomic neuropathy, aseptic meningitis, encephalitis, transverse myelitis	Physical examination: sensory changes, lack of tendon reflexes; Neuroimaging testing, nerve conduction testing; Nerve/muscle biopsy	G1: Closely monitor nerve function and use glucocorticoids if necessary	Suspend immunotherapy; (transverse myelitis requires permanent discontinuation)
			G2: Use the glucocorticoid prednisone or similar drugs at a daily dose of 1 to 2 mg/kg	Suspend immunotherapy; (transverse myelitis and Guillain-Barré syndrome require permanent discontinuation)
			G3-4: High-dose glucocorticoid (2 to 4 mg/kg methylprednisolone or similar drugs daily)	Permanently discontinue immunotherapy

Potential immunity-related adverse events	Common symptoms and signs	Assessment and diagnosis methods	Recommended management method	Dose adjustment
Musculoskeletal toxicity	Inflammatory arthritis, myositis, polymyalgia	Nervous system diseases and rheumatology examinations; Laboratory tests such as hematology and autoantibodies; When the diagnosis is unclear, consider EMG, MRI and/or biopsy alone; Emergency consultation with rheumatologists and neurologists	G1: Oral glucocorticoid therapy; if no contraindications, consider acetaminophen or non-steroidal anti-inflammatory analgesics	Continue immunotherapy
			G2: Glucocorticoid therapy; if necessary, give non-steroidal anti-inflammatory drugs; consultation with rheumatologists and neurologists	Suspend immunotherapy; (if the patient presents with elevated enzymes, abnormal electromyography, abnormal muscle MRI or abnormal biopsy, permanently discontinue immunotherapy)
			G3-4: Consultation with rheumatologists and neurologists; Glucocorticoids; plasma exchange; consider IVIG treatment; if symptoms and CK levels do not improve or worsen within 4-6 weeks, consider other immunotherapies such as methotrexate, azathioprine, or mycophenolate mofetil; use rituximab with caution	Suspend immunotherapy until recovery to grade 1 or below (if the myocardium is involved, permanently stop immunotherapy)
Hematological toxicity	Autohemolytic anemia, idiopathic thrombocytopenic purpura, hemolytic uremic syndrome, aplastic anemia, lymphopenia, immune	Medical history and systematic physical examination; Laboratory tests such as peripheral blood and autoimmune antibodies;	G1: Closely monitor laboratory parameters	Continue immunotherapy; (acquired TTP, aplastic anemia, and acquired

Potential immunity-related adverse events	Common symptoms and signs	Assessment and diagnosis methods	Recommended management method	Dose adjustment
	thrombocytopenia, acquired hemophilia	Rule out other causes (tumor-related, infectious, other drug-related, etc.)		hemophilia require suspending of immunotherapy)
			G2: Prednisone 0.5-1 mg/kg/d or similar drugs	Suspend immunotherapy
			G3-4: Hospitalization; hematology consultation; prednisone 1-2 mg/kg/d or similar drugs; if poor efficacy of glucocorticoids, consider other immunotherapy drugs such as rituximab, IVIG, cyclosporine A, mycophenolate mofetil, etc.; blood products for supportive care.	Permanently discontinue immunotherapy
Ocular toxicity	Uveitis, iritis, episcleritis, blepharitis	Collection of past medical history; Special examination of ophthalmology; Accompanied by symptoms or signs	G1: Asymptomatic	Continue immunotherapy
			G2: Medical intervention indicated	Suspend immunotherapy
			G3-4: Significantly symptomatic	Permanently discontinue immunotherapy
Other immune-mediated adverse reactions	Such as pancreatitis, adrenal insufficiency, rhabdomyolysis, etc.		G1-2 (mild to moderate)	Suspend immunotherapy until the adverse event has reverted to grade 1 or below
			G3-4 (severe or life-threatening)	Permanently discontinue immunotherapy