Supplementary Information

Title: Liposomal mitoxantrone plus tislelizumab in patients with relapsed or refractory extranodal natural killer/T-cell lymphoma: a phase 1b/2 trial

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Supplementary tables

Supplementary Table 1. Prior treatment regimens before study enrollment (n=40)

Prior treatment regimens	Number
P-GemOx-based regimens	**36**
P-GemOx plus anti-PD-1	14
P-GemOx	7
P-GemOx in combination with radiotherapy	7
P-GemOx plus ASCT	4
P-GemOx plus anti-PD-1 in combination with radiotherapy	1
P-GemOx plus chidamide	1
P-GemOx plus etoposide	1
P-GemOx plus dexamethasone	1
Asparaginase-based regimens	**13**
Asparaginase plus anti-PD-1 and chidamide	2
Asparaginase plus anti-PD-1 in combination with radiotherapy	1
Asparaginase plus anti-PD-1	1
GEPD in combination with radiotherapy	1
GEPD plus anti-PD-1 in combination with radiotherapy	1
Asparaginase, anti-PD-1, dexamethasone and linperlisib	1
Asparaginase plus EPOCH in combination with ASCT	1
Asparaginase, anti-PD-1, cyclophosphamide, vincristine, and etoposide	1
Asparaginase, anti-PD-1, vincristine, and prednisone	1
Asparaginase, cyclophosphamide, vinorelbine, etoposide, and prednisone	1
Asparaginase, cyclophosphamide, vincristine, etoposide, and prednisone	1
Asparaginase, methotrexate, dexamethasone, and etoposide	1
Other regimens	**7**
Anti-PD-1 plus chidamide	3
Anti-PD-1 plus chidamide in combination with radiotherapy	1
Cyclophosphamide, doxorubicin, vincristine, and prednisone	1
Golidocitinib	1
Doxorubicin, etoposide, and methylprednisolone	1

Data are shown as number.

ASCT: autologous stem cell transplantation; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; GEPD: asparaginase, gemcitabine, etoposide, and dexamethasone; P-GemOx: pegaspargase, gemcitabine, and oxaliplatin.

Supplementary Table 2. Anti-tumor activity in the per-protocol set (n=38)

	Dose-escalation phase (n=6)	Dose-expansion phase (n=32)	Total (n=38)
Best response*			
Complete response	5 (83%; 42%)	16 (50%; 34%)	21 (55%; 41%)
Partial response	1 (17%; 0%-64%)	7 (22%; 9%-40%)	8 (21%; 10%-37%)
Stable disease	0	2 (6%; 1%-20%)	2 (5%; 1%-18%)
Progressive disease	0	7 (22%; 9%-40%)	7 (18%; 8%-34%)
Objective response rate	6 (100%; 54%-100%)	23 (72%; 53%-86%)	29 (76%; 60%-89%)
Disease control rate	6 (100%; 54%-100%)	25 (78%; 60%-91%)	31 (82%; 66%-92%)

Data are shown as number (%, 95 % confidence interval), except complete response, which is shown as number (%, one-sided 95% lower confidence bound). *Best response was defined as the best response achieved at any time during treatment according to the Lugano 2014 criteria. Percentages may not add to 100 due to rounding.

Supplementary Table 3. Subsequent regimens after failure of Lipo-MIT plus tislelizumab (n=18)

Regimens	Number
Immunotherapy-based regimens	
Anti-PD-1 antibody plus anti-LAG3 antibody	5
Anti-PD-1/TIGIT bispecific antibody plus JAK inhibitor	1
Anti-PD-1/CTLA-4 bispecific antibody plus chidamide and azacitidine	1
Anti-PD-1 antibody plus chidamide	1
Anti-PD-1 antibody plus chidamide and selinexor	1
Anti-PD-1 antibody plus linperlisib	1
Chemotherapy regimens	
IMVP-16 regimen	1
MESA regimen	1
Modified SMILE regimen plus selinexor	1
Pegaspargase, ifosfamide, etoposide and selinexor	1
Pegaspargase plus Lipo-MIT and dexamethasone	1
Methotrexate	1
Small molecule targeted drug	
Golidocitinib	1
Bromodomain inhibitor	1

IMVP-16 regimen: ifosfamide, methotrexate, etoposide, and prednisone; MESA regimen: methotrexate, etoposide, dexamethasone, and pegaspargase; Modified SMILE regimen: dexamethasone, methotrexate, ifosfamide, pegaspargase, and etoposide.

Supplementary Table 4. Adverse events in phase 1b (n=6)

	Grade 1	Grade 2	Grade 3	Grade 4
Hematological toxicities				
Leukopenia	0	1 (17%)	2 (33%)	2 (33%)
Neutropenia	0	2 (33%)	1 (17%)	2 (33%)
Anemia	4 (67%)	1 (17%)	0	0
Lymphopenia	1 (17%)	2 (33%)	0	1 (17%)
Thrombocytopenia	0	1 (17%)	0	1 (17%)
Febrile neutropenia	0	0	2 (33%)	0
Non-hematological toxicities				
Hyperglycemia	4 (67%)	0	0	0
Pigmentation	4 (67%)	0	0	0
Hypothyroidism	0	1 (17%)	0	0
Albumin decreased	2 (33%)	0	0	0
Fever	1 (17%)	0	0	0
AST increased	0	1 (17%)	0	0
Infection[#]	0	2 (33%)	0	0
ALT increased	1 (17%)	0	1 (17%)	0
Anorexia	0	1 (17%)	0	0
Hyponatremia	2 (33%)	0	0	0
Hypokalemia	3 (50%)	0	0	0
Hypocalcemia	1 (17%)	0	0	0
Rash	2 (33%)	0	0	0
Nausea or vomiting	0	1 (17%)	0	0
Diarrhea	0	0	1 (17%)	0
Alkaline phosphatase increased	1 (17%)	0	0	0
Pruritus	2 (33%)	0	0	0
Headache	0	1 (17%)	0	0

Data are shown as number (%). [#]Infections included COVID-19 infection (n=1) and intestinal infection (n=1).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Supplementary Table 5. Adverse events in phase 2 (n=34)

	Grade 1	Grade 2	Grade 3	Grade 4
Hematological toxicities				
Leukopenia	1 (3%)	7 (21%)	17 (50%)	0
Neutropenia	1 (3%)	9 (26%)	10 (29%)	3 (9%)
Anemia	13 (38%)	7 (21%)	3 (9%)	0
Lymphopenia	3 (9%)	2 (6%)	12 (35%)	1 (3%)
Thrombocytopenia	4 (12%)	3 (9%)	0	1 (3%)
Febrile neutropenia	0	0	5 (15%)	0
Non-hematological toxicities				
Hyperglycemia	10 (29%)	0	1 (3%)	0
Pigmentation	10 (29%)	0	0	0
Hypothyroidism	9 (26%)	4 (12%)	0	0
Albumin decreased	11 (32%)	1 (3%)	0	0
Fever	8 (24%)	3 (9%)	0	0
AST increased	6 (18%)	2 (6%)	1 (3%)	0
Infection[#]	1 (3%)	3 (9%)	3 (9%)	0
ALT increased	5 (15%)	0	1 (3%)	0
Anorexia	4 (12%)	1 (3%)	1 (3%)	0
Hyponatremia	4 (12%)	0	1 (3%)	0
Hypokalemia	3 (9%)	0	0	0
Hypocalcemia	5 (15%)	0	0	0
Rash	2 (6%)	2 (6%)	0	0
Fatigue	4 (12%)	1 (3%)	0	0
Nausea or vomiting	2 (6%)	0	1 (3%)	0
Diarrhea	3 (9%)	0	0	0
Infusion reaction	0	4 (12%)	0	0
Alkaline phosphatase increased	3 (9%)	0	0	0
Pruritus	1 (3%)	1 (3%)	0	0
Blood bilirubin increased	2 (6%)	0	1 (3%)	0
Headache	1 (3%)	0	0	0
Blood creatinine increased	2 (6%)	0	0	0
Palpitations	2 (6%)	0	0	0
Atrial fibrillation	0	1 (3%)	0	0
QT interval prolonged	1 (3%)	0	0	0
Oral ulcer	1 (3%)	0	0	0
Hyperthyroidism	1 (3%)	0	0	0
Eczema	0	1 (3%)	0	0
Herpes zoster	0	1 (3%)	0	0

Data are shown as number (%). [#]Infections included lung infection (n=4), COVID-19 infection (n=1), and urinary tract infection (n=2).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Supplementary Table 6. Immune-related adverse events in the safety analysis set (n=40)

	Grade 1	Grade 2	Grade 3	Grade 4	Any grade
Hypothyroidism	9 (23%)	5 (13%)	0	0	14 (35%)
Rash	4 (10%)	2 (5%)	0	0	6 (15%)
Pruritus	3 (8%)	1 (3%)	0	0	4 (10%)
Hyperthyroidism	1 (3%)	0	0	0	1 (3%)

Data are shown as number (%).

Supplementary Table 7. Reasons for treatment interruptions (n=14)

Treatment-related adverse event	Number (%)
Neutropenia or febrile neutropenia	6 (43%)
Leukopenia	2 (14%)
COVID-19 infection	2 (14%)
Thrombocytopenia	1 (7%)
ALT, AST and bilirubin elevated	1 (7%)
Diarrhea	1 (7%)
Hypothyroidism	1 (7%)

Data are shown as number (%).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Supplementary Table 8. Reasons for Lipo-MIT dose reduction (n=4)

Treatment-related adverse event	Number (%)
Neutropenia	2 (50%)
Febrile neutropenia	1 (25%)
Thrombocytopenia	1 (25%)

Data are shown as number (%).

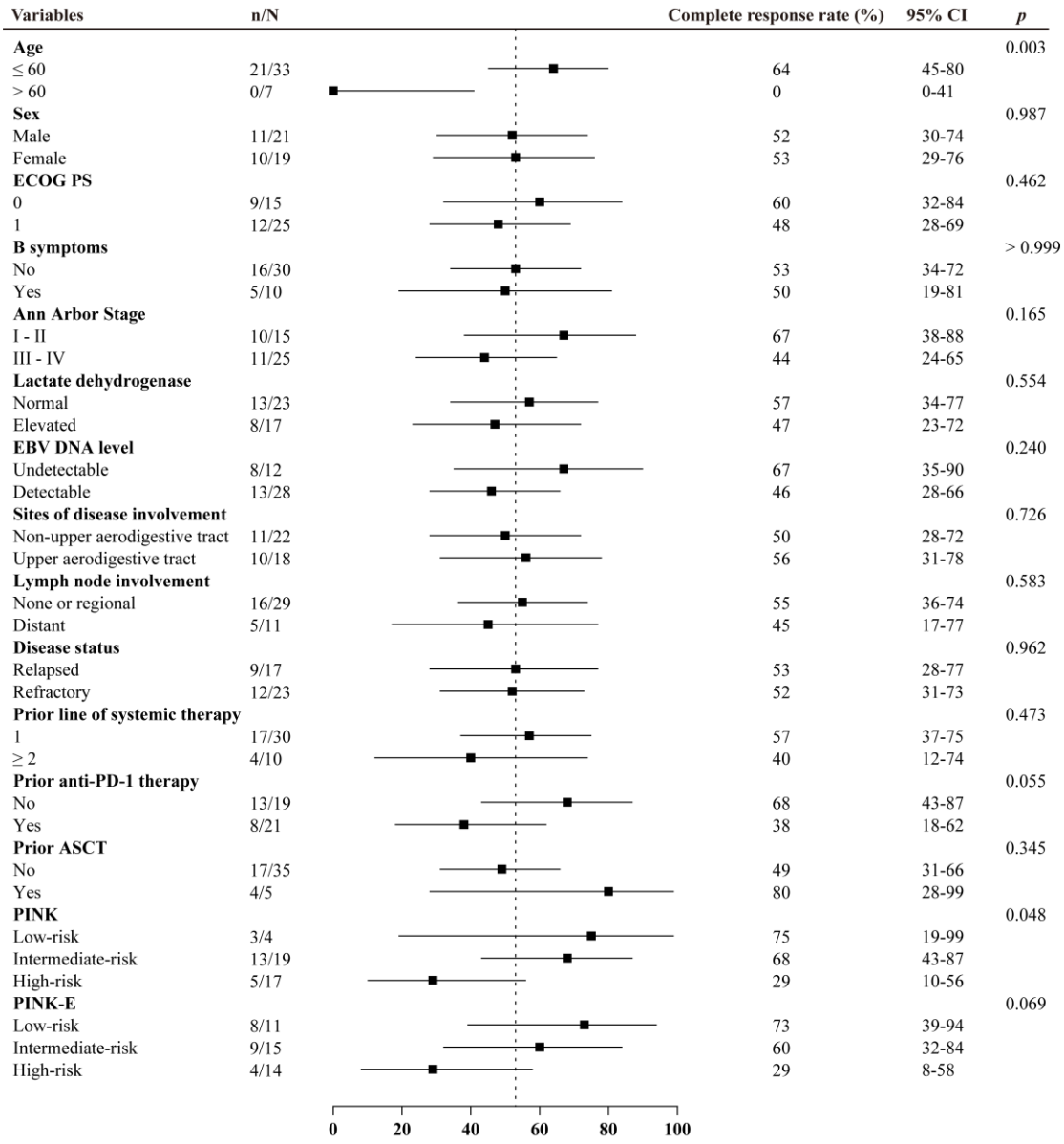
Supplementary Table 9. Baseline immune cell infiltration according to response and disease progression

	Total (n=25)	Response		Disease progression	
		CR (n=12)	Non-CR (n=13)	PD (n=19)	Non-PD (n=6)
$CD8^+$ T cell proportion (%)	10.0 (5.9–15.6)	12.8 (9.9–19.4)	7.3 (2.2–10.6)	8.7 (3.3–11.6)	16.3 (13.1–19.6)
$CD8^+$ T cell density (cells /mm^2)	821 (246–1267)	1072 (816–1409)	454 (227–821)	619 (235–960)	1320 (986–1571)
PD-1^+CD8^+ T cell proportion (%)	0.5 (0.1–1.2)	1.1 (0.4–1.2)	0.2 (0.1–1.2)	0.2 (0.1–1.2)	1.2 (0.7–1.3)
PD-1^+CD8^+ T cell density (cells /mm^2)	26 (8–77)	57 (24–92)	10 (5–26)	13 (7–71)	62 (33–123)
PD-$L1^+CD56^+$ cell proportion (%)	1.4 (0.4–2.2)	2.1 (1.2–2.3)	0.4 (0.2–1.4)	1.2 (0.3–2.1)	1.8 (0.7–2.4)
PD-$L1^+CD56^+$ cell density (cells /mm^2)	77 (22–140)	115 (56–199)	29 (18–121)	57 (19–140)	83 (55–191)
PD-1^+CD56^+ cell proportion (%)	0.1 (0.1–0.5)	0.4 (0.1–1.3)	0.1 (0.1–0.1)	0.1 (0.1–0.4)	0.3 (0.1–0.6)
PD-1^+CD56^+ cell density (cells /mm^2)	11 (2–38)	39 (9–87)	7 (2–11)	9 (4–29)	25 (4–42)
PD-$L1^+$ cell proportion (%)	9.0 (4.2–16.8)	13.9 (7.8–31.1)	8.1 (2.4–14.5)	10.2 (5.8–21.4)	8.1 (3.8–14.9)
PD-$L1^+$ cell density (cells /mm^2)	757 (199–1534)	991 (471–2121)	709 (177–1245)	757 (281–1646)	598 (198–1032)

Data are shown as median (interquartile range). Cell proportion was defined as the percentage of marker-positive cells relative to total nucleated cells. Cell density was defined as the number of marker-positive cells per mm^2. Statistical comparisons between groups are shown in Supplementary Figure 2 and 3. Abbreviations: CR, complete response; Non-CR, non-complete response; Non-PD, non-progressive disease; PD, progressive disease.

Supplementary Table 10. Treatment cycles and reasons for discontinuation in patients aged >60 years (n=7)

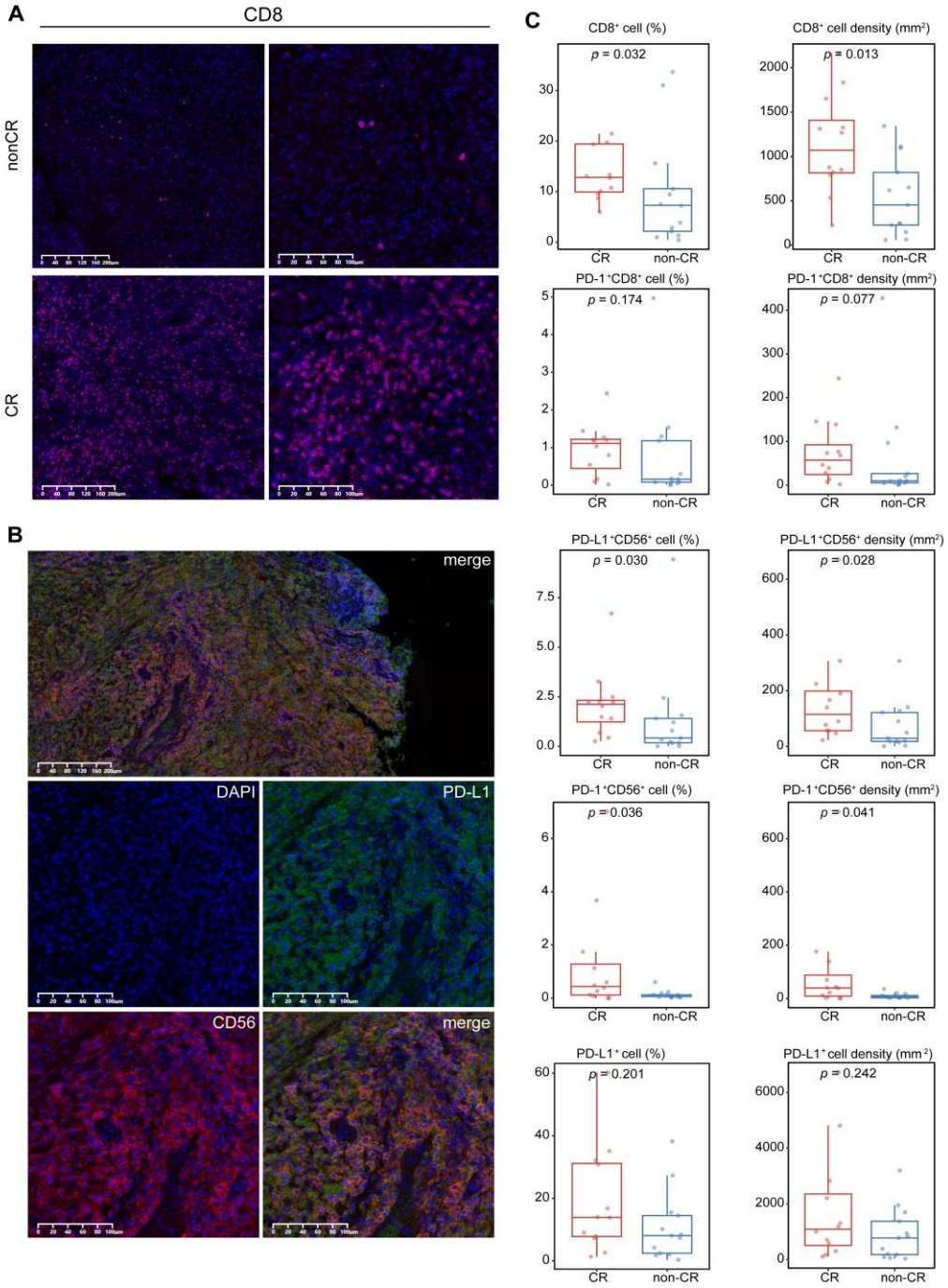
Treatment cycles	Number (%)
One cycle (n=4, 57%)	
Disease progression	2 (29%)
Withdrawal of consent	1 (14%)
Loss to follow up	1 (14%)
Two cycles (n=1, 14%)	
Investigator decision due to an increase of < 50% in the sum of the product of the diameters (SPD) despite stable disease	1 (14%)
Three cycles (n=1, 14%)	
Withdrawal of consent	1 (14%)
Six cycles (n=1, 14%)	
Disease progression	1 (14%)



Supplementary Figure 1. Forest plot showing post-hoc analyses of complete response rate (n=40)

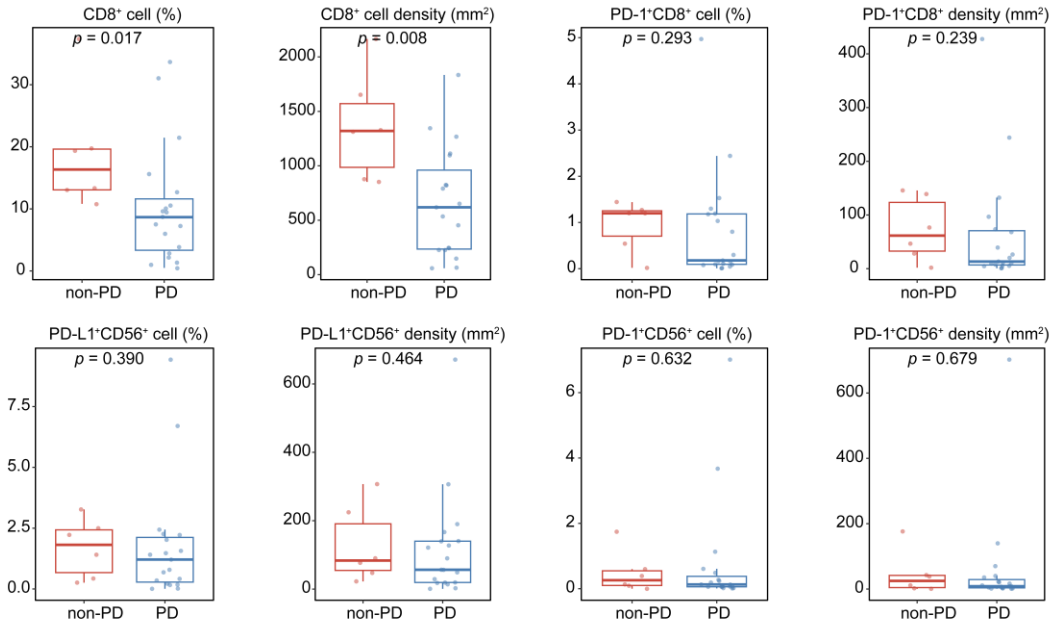
P values were calculated using chi-square test or Fisher's exact test as appropriate.

Abbreviations: ASCT, autologous stem cell transplantation; CI, confidence interval; EBV, Epstein Barr virus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-1, programmed cell death protein-1; PINK, the prognostic index of natural killer/T-cell lymphoma; PINK-E, the prognostic index for natural killer/T-cell lymphoma-Epstein Barr virus.



Supplementary Figure 2. Association between treatment response and immune cell components in the tumor microenvironment.

(A) Multiplex immunofluorescence staining for CD8 according to CR status. Scale bars, 200 μm (left panels) and 100 μm (right panels). (B) Multiplex immunofluorescence staining for PD-L1 and CD56. Scale bars, 200 μm (top merged image) and 100 μm (bottom panels). (C) The bar charts showing the proportions and densities of $CD8^+$, $PD\text{-}1^+CD8^+$, $PD\text{-}L1^+CD56^+$, $PD\text{-}1^+CD56^+$, and $PD\text{-}L1^+$ cells according to CR status (CR, n=12; non-CR, n=13). Data are presented as median ± interquartile range. *P* values were calculated using the Mann-Whitney U test. Source data are provided as a Source Data file. Abbreviations: CR, complete response; non-CR, non-complete response.



Supplementary Figure 3. Association between disease progression and immune cell components in the tumor microenvironment.

The bar charts show the proportions and densities of $CD8^+$, $PD\text{-}1^+CD8^+$, $PD\text{-}L1^+CD56^+$, and $PD\text{-}1^+CD56^+$ cells according to disease progression status (non-PD, n=6; PD, n=19). Data are presented as median ± interquartile range. *P* values were calculated using the Mann-Whitney U test. Source data are provided as a Source Data file.

Abbreviations: non-PD, non-progressive disease; PD, progressive disease.

Supplementary Note 1. List of site investigators

Trial site name and address	Patients	Ethics committees	Investigators
Sun Yat-sen University Cancer Center Department of Medical Oncology Guangzhou, 510060, P.R. China	25	Ethics committee of Sun Yat-sen University Cancer Center	Qingqing Cai, Yi Xia, Huiqiang Huang
Beijing Tongren Hospital, Capital Medical University Department of Hematology Beijing, 100730, P.R. China	5	Ethics committee of Beijing Tongren Hospital, Capital Medical University	Liang Wang
The First Affiliated Hospital, Zhejiang University School of Medicine Department of Hematology Hangzhou, 310003, P.R. China	2	Ethics committee of The First Affiliated Hospital, Zhejiang University School of Medicine	Hongyan Tong
Daping Hospital, Army Medical University Department of Hematology Chongqing, 400042, P.R. China	2	Ethics committee of Army Medical University Daping Hospital	Dongfeng Zeng
The First People's Hospital of Foshan Department of Hematology Foshan, 528000, P.R. China	2	Ethics committee of The First People's Hospital of Foshan	Ying Zhao
Jiangxi Cancer Hospital Department of Lymphatic and Hematological Oncology Nanchang 330029, P.R. China	1	Ethics committee of Jiangxi Cancer Hospital	Yuerong Shuang
The Second Hospital of Dalian Medical University Department of Medical	1	Ethics committee of The Second	Xiuhua Sun, Xiaobo Wang

Oncology, and Department of Hematology Dalian, 116023, P.R. China		Hospital of Dalian Medical University	
Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology Department of Hematology Wuhan, 430030, P.R. China	1	Ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology	Zhenya Hong
The First Affiliated Hospital of Guangxi Medical University Department of Medical Oncology Nanning, 530021, P.R. China	1	Ethics committee of The First Affiliated Hospital of Guangxi Medical University	Zhigang Peng
Fujian Cancer Hospital Department of Lymphoma and Head & Neck Tumors Fuzhou, 350014, P.R. China	1	Ethics committee of Fujian Cancer Hospital	Yu Yang
The Fifth Affiliated Hospital of Guangzhou Medical University Department of Hematology Guangzhou, 510700, P.R. China	1	Ethics committee of The Fifth Affiliated Hospital of Guangzhou Medical University	Runhui Zheng Jianbo Liu
Qilu Hospital of Shandong University Department of Hematology Jinan, 250012, P.R. China	/	Ethics committee of Qilu Hospital of Shandong University	Jingjing Ye
Peking Union Medical College Hospital Department of Hematology	/	Ethics committee of Peking Union Medical College	Wei Zhang

Beijing, 100730, P.R. China		Hospital	
Fujian Medical University Union Hospital Department of Hematology Fuzhou, 350001, P.R. China	/	Ethics committee of Fujian Medical University Union Hospital	Jianzhen Shen
Fudan University Shanghai Cancer Center Department of Lymphoma Shanghai, 200032, P.R. China	/	Ethics committee of Fudan University Shanghai Cancer Center	Rong Tao
Guangxi Medical University Cancer Hospital Department of Lymphohematology and Pediatric Oncology Nanning, 530021, P.R. China	/	Ethics committee of Guangxi Medical University Cancer Hospital	Hong Cen

Supplementary Note 2. Protocol

Tislelizumab combined with liposomal mitoxantrone in patients with relapsed/refractory extranodal NK/T cell lymphoma (ENKTL): a single-arm, open-label, multicenter, phase 1b/2 trial

Version number: 1.2

Version date: February 10, 2025

Lead institution: Sun Yat-sen University Cancer Center

CONFIDENTIAL

The information contained in this article is confidential and the property of the sponsor of the study. The purpose of this protocol is to provide the relevant information. An investigator may disclose the protocol to the trial participants or investigator institutional review board, ethics committee, or pharmaceutical regulatory board for the same purpose, provided that the following conditions are met. The contents of the protocol may not be used in any other clinical study or disclosed to any other person or group without the prior written permission of the sponsor. Although this condition does not apply to disclosure required by government regulations, investigators must notify the sponsor in a timely manner. In addition, any supplementary information of the protocol is also confidential and belongs to the sponsor of the study, and its confidentiality is the same as the protocol content.

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PROTOCOL SYNOPSIS

Title	Tislelizumab combined with liposomal mitoxantrone in patients with relapsed/refractory extranodal NK/T cell lymphoma (ENKTL): a single-arm, open-label, multicenter, phase 1b/2 trial
Objectives	To evaluate the efficacy and safety of tislelizumab combined with liposomal mitoxantrone in the treatment of relapsed/refractory extranodal NK/T-cell lymphoma.
Study design	This was a single-arm, open-label, multicenter, phase 1b/2 clinical study
Drugs	Liposomal mitoxantrone; tislelizumab
Population	Relapsed/refractory extranodal NK/ T-cell lymphoma
Inclusion criteria	1. ENKTL confirmed by histopathology at the study center; 2. Willingness to participate in trial; Fully understand and be informed of the study and sign written informed consent; 3. Age of 18-75 years at the time of enrollment; 4. Patients with refractory or relapsed ENKTL who had failed asparaginase-based chemotherapy or chemoradiotherapy. Refractory disease was defined as: i) failure to achieve a complete response after asparaginase-based chemotherapy; or ii) disease progression within 6 months after the last asparaginase-containing regimen; Relapsed disease was defined as recurrence of lymphoma after achieving complete response after initial therapy; 5. Eastern Cooperative Oncology Group performance status of 0-2; 6. Estimated life expectancy ≥3 months; 7. At least one measurable lesion according to the Lugano 2014 criteria;

	8. No evidence of hemophagocytic lymphohistiocytosis (HLH). Patients with clinically diagnosed HLH could be enrolled only after receiving therapy for HLH and being assessed by the investigator as clinically stable and suitable for study participation; 9. Adequate organ and bone marrow function, defined as follows: a) Bone marrow function: absolute neutrophil count (ANC) ≥ 1.5×10^9/L (≥1.0×10^9/L for patients with bone marrow involvement), platelet count (PLT) ≥ 75×10^9/L (≥50×10^9/L for patients with bone marrow involvement), and hemoglobin (HGB) ≥ 8.0 g/dL; No receipt of granulocyte colony-stimulating factor, platelet transfusion, or red blood cell transfusion within 14 days prior to enrollment; b) Hepatic function: Total bilirubin (TBIL) ≤1.5× upper limit of normal (ULN) (≤3.0×ULN if with liver involvement); alanine aminotransferase (ALT) and aspartate transferase (AST) ≤2.5×ULN (≤5.0×ULN if with liver involvement); c) Renal function: serum creatinine (Cr) ≤1.5×ULN; d) Coagulation function: International normalized ratio (INR) ≤1.5 × ULN; Prothrombin time (PT) and activated partial thromboplastin time (APTT) ≤1.5×ULN, unless the patient is receiving anticoagulant therapy and the values fall within the expected therapeutic range; e) Thyroid function: Thyroid-stimulating hormone (TSH) or free thyroxine (FT4) or free triiodothyronine (FT3) were within the normal range ±10% (note: patients with non–autoimmune thyroid disorders, or those receiving stable replacement therapy with FT3/FT4 within the normal range, were eligible);

Exclusion criteria	1. Prior treatment with liposomal mitoxantrones, or a cumulative dose of doxorubicin > 360 mg/m^2 or a cumulative dose of mitoxantrone > 160mg/m^2; 2. History of another malignancy within the past 5 years, or concurrent malignancy, with the exception of adequately treated basal cell carcinoma of the skin; 3. Aggressive NK-cell leukemia or central nervous system invasion; 4. Participation in another investigational drug clinical trial within 4 weeks prior to the start of study treatment; 5. Receipt of any anticancer therapy within 4 weeks prior to study treatment initiation; 6. Receipt of allogeneic hematopoietic stem-cell transplantation within 3 years before the administration of the study treatment (patients were eligible if they had undergone allogeneic hematopoietic stem-cell transplantation more than 3 years before the administration of the study drug and did not have current graft-versus-host reactions); receipt of autologous hematopoietic stem-cell transplantation within 100 days before the administration of the study treatment; 7. Patients with a known history of human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome; 8. Patients with active chronic hepatitis B or active hepatitis C infection. Patients positive for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBc Ab), or hepatitis C antibody (HCV Ab) must undergo further HBV DNA (≤1000 copies/mL or ≤500 IU/mL) and HCV RNA testing (below the lower limit of detection). Patients may be enrolled only after exclusion of active infection. HBV carriers, patients with medically controlled HBV (HBV DNA ≤1000 copies/mL or ≤500 IU/mL), and those with cured HCV infection could be included.

	9. Patients who were receiving systemic glucocorticoids or other immunosuppressive therapy within 14 days prior to study treatment (Topical, ophthalmic, intra-articular, intranasal, or inhaled corticosteroids with minimal systemic absorption are permitted. Short-term [≤7 days] corticosteroid use for prophylaxis—e.g., contrast allergy—or for non-autoimmune conditions is allowed); 10. Active autoimmune disease requiring systemic treatment within the past 2 years (Patients with conditions controlled on replacement therapy only—e.g., type 1 diabetes, hypothyroidism on hormone replacement, or adrenal/pituitary insufficiency on physiological glucocorticoids—could be included); 11. Cardiac dysfunction and disease, including any of the following: a) Long QTc syndrome or QTc interval >480 ms; b) Complete left bundle branch block, or second- or third-degree atrioventricular block; c) Severe, uncontrolled arrhythmias requiring medical treatment; d) NYHA class ≥ III heart failure; e) Left ventricular ejection fraction (LVEF) < 50%; f) History of myocardial infarction, unstable angina, clinically significant ventricular arrhythmias or other arrhythmia requiring treatment, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities within 6 months before enrollment; 12. Major surgery within 28 days before enrollment, or presence of unhealed wounds or incompletely healed fractures;

	13. Receipt of a live attenuated vaccine within 4 weeks before enrollment or planned during the study (except influenza vaccine); 14. Pregnancy or breastfeeding, or women and men of childbearing potential unwilling to use effective contraception; 15. Psychiatric illness or cognitive impairment that would preclude provision of informed consent; 16. Active infection, except tumor-related fever (B symptoms).
Treatment	This is a single-arm, open-label, multicenter, phase 1b/2 study in patients with relapsed and refractory ENKTL who were given different doses of liposomal mitoxantrone and fixed doses of tislelizumab. The aim of this trial is to explore the safety of the combination regimen, and determine the optimal dose of liposomal mitoxantrone in the combination regimen. At the same time, the efficacy and safety of the combined regimen were evaluated. The study was divided into dose-escalation phase and dose-expansion phase. The study included a screening period, induction therapy period, maintenance therapy period, and follow-up period. **I. Screening period** After signing the informed consent form and completing all baseline examinations during the screening period, eligible participants will proceed to the treatment phase. **II. Induction therapy period** **Dose-escalation phase of the study** Participants will receive tislelizumab in combination with liposomal mitoxantrone. Tislelizumab will be administered at a fixed dose, whereas the dose of liposomal mitoxantrone will be escalated sequentially from the lower to the higher dose levels. The treatment

	regimen will be administered once every 4 weeks. The first cycle of treatment will serve as the dose-limiting toxicity (DLT) observation period. Participants who complete the 4-week treatment and observation of cycle 1 may proceed to subsequent cycles, until the occurrence of relapse or progression, death, withdrawal of consent, initiation of alternative therapy, or completion of the study—whichever occurs first. Relevant clinical assessments will be performed throughout the study to evaluate safety and tolerability. 1. Dose-escalation protocol · In the dose-escalation phase, 16 mg/m^2 of liposomal mitoxantrone was used as the initial dose, and two dose groups of 16 mg/m^2 and 20 mg/m^2 were designed. · Tislelizumab was given at a fixed dose of 200 mg, q4w. · Principle of dose-escalation (1) Dose escalation followed the "3 + 3" design. Each dose level enrolled 3–6 patients, and safety and tolerability were assessed during the first treatment cycle. If no DLT occurred among the first three patients, the trial proceeded to the next higher dose level as planned. If one DLT occurred, three additional patients were enrolled at the same dose level; escalation continued if no further DLTs were observed. If two or more DLTs occurred at a given dose level, the preceding dose level was defined as the maximum tolerated dose (MTD). (2) At least 6 patients were required to complete DLT observation at the MTD dose. (3) Patients who developed a DLT were managed according to standard clinical practice at the discretion of the investigator. Treatment could

	be delayed by up to 2 weeks, and patients could resume therapy at the same dose or at a reduced dose level in the subsequent cycle. (4) If more than one patient experienced a DLT at the lowest prespecified dose (16 mg/m²), the investigator and sponsor could jointly consider exploring a lower dose (12 mg/m²). Conversely, if no MTD was identified at the highest prespecified dose (20 mg/m²), the investigator and sponsor could discuss whether to continue escalation to higher dose levels. 2．Dose-limiting toxicities (DLTs) DLTs were defined as adverse events considered related to the investigational drug that occurred within the first 28 days after initial administration (Cycle 1, Day 1–28), and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE v5.0). 3. Maximum tolerated dose (MTD) The MTD was defined as the highest dose level at which no more than 33% of patients experienced a DLT, with at least six patients evaluable for DLT assessment at that dose level. 4. Recommended phase 2 dose (RP2D) If an MTD of liposomal mitoxantrone hydrochloride was identified, the MTD was selected as the RP2D. If no MTD was reached, the RP2D was determined jointly by the investigators and the sponsor based on safety data from the DLT observation period during dose escalation. The RP2D was used for enrollment during the dose-expansion phase. **Dose-expansion phase of the study**

	To explore the efficacy, safety and tolerability of liposomal mitoxantrone combined with tislelizumab at the RP2D dose level. Tumor assessments were performed every two cycles during induction therapy. **III. Maintenance therapy period** After completion of six induction cycles, tumor response was assessed. Participants achieving complete response (CR), partial response (PR), or stable disease (SD) proceeded to maintenance therapy. Tislelizumab was administered at 200 mg on Day 1 every 3 weeks (q3w) and continued until disease progression, unacceptable toxicity, or with a maximum total treatment duration of 12 months, whichever occurred first. Tumor assessments were conducted every 3 months during the maintenance phase. **IV. Follow-up period** An end-of-treatment visit occurred 4 weeks after the last dose. Follow-up was planned every 3 months during the first 2 years, every 6 months during years 3 to 5, and yearly thereafter.
Study duration	Anticipated date for first patient enrollment: May 2022; Anticipated completion of enrollment: November 2024; Anticipated end date of follow-up: November 2025.
Endpoints	➢ Primary endpoints • Dose-escalation phase To evaluate the DLTs of liposomal mitoxantrone combined with tislelizumab, and explore the RP2D. • Dose-expansion phase

	To evaluate the efficacy of tislelizumab combined with liposomal mitoxantrone in relapsed/refractory ENKTL, which is the complete response rate. ➢ Secondary endpoints • Dose-escalation phase 1. Safety and adverse events (according to NCI CTC AE v5.0); 2. Laboratory examination; CR rate, objective response rate (ORR), disease control rate [DCR: CR+PR+ stable disease (SD)]. • Dose-expansion phase 1. ORR, DCR, progression-free survival (PFS) and overall survival (OS). 2. Safety. ➢ Exploratory endpoints To explore the correlation between biomarkers and the efficacy of tislelizumab combined with liposomal mitoxantrone treatment
Sample size	1. Dose-escalation phase: 6 to 12 patients were planned to be enrolled; 2. Dose-expansion phase: A single-stage design method was used to determine the sample size. The null hypothesis assumed a complete response rate of 28% for lipo-MIT monotherapy, and an estimated target complete response rate of 50% for patients treated with lipo-MIT combined with tislelizumab. Therefore, based on an exact binomial test with a one-side α of 0.05 and 80% power, a sample size of 32 patients was required. The null hypothesis would be rejected if at least 14 patients achieved complete response. Allowing for a 10% dropout rate, the planned sample size was 36 patients. In total, 42 to 48 patients were enrolled in phase 1b and 2 of this study.

SCHEDULE OF ASSESSMENTS

Assessment	Screening period	Induction therapy period	Maintenance therapy period	Follow-up period
Days	Before treatment	Cycles 1-6 CnD1	Cycle 7 to 1 year CnD1	every 3 months during the first 2 years, every 6 months during years 3 to 5, and yearly thereafter
Time window	-28D to -1D	±3D	±3D	±7D
Informed consent [a]	x			
Inclusion/exclusion criteria	x			
Demographics and medical history	x			
Underlying diseases and treatment	x			
Physical examination	x	x	x	x
Imaging of the lesion can be evaluated [b]	x	X (every 2 cycles)	x (every 3 months)	x
Blood routine	x	x	x	
Liver function [c]	x	x	x	
Electrolytes [d]	x	x	x	
Renal function [e]	x	x	x	
Fasting blood glucose	x	x	x	
Thyroid function [f]	x	x	x	
Urine routine	x	x	x	

Infectious disease screening [g]	x			
Pregnancy testing [h]	x			
EBV DNA	x			
Concomitant therapy	x	Keep a record	Keep a record	
ECG (while calculating QTc)	x	x	x	
Markers of myocardial damage and heart failure [i]	x	x	x	x
Echocardiogram	x	x (Every 8 weeks)	(x)	
Adverse event		x	x	x
Mitoxantrone hydrochloride liposome injection		x		
Tislelizumab		x	x	
Treatment after disease progression		Keep a record	Keep a record	x
Evaluation of Efficacy		x	x	x
NYHA cardiac function classification	x	x	x	x
Survival status				x
Tumor tissue samples [j]	x			
Peripheral blood sample [k]	x	x	x	

Notes:

a. Informed consent forms must be obtained prior to entering the screening period.

b. Participants underwent imaging assessments at scheduled times until radiographic progression, initiation of new antineoplastic therapy, withdrawal of consent, death, or the end of the study, whichever occurred first. Imaging included PET-CT or contrast-enhanced CT and/or MRI (nasopharyngeal, neck, chest, upper and lower abdomen, and pelvis), brain MRI was required when brain metastases were suspected (CT could be used instead if MRI was contraindicated), and during the screening period, tumor assessment could be extended to imaging findings obtained within 4 weeks before the administration of treatment and informed consent was obtained. As long as there is a measurable/measurable lesion, it can be used for screening tumor assessment, and the non-measurable lesion can be re-examined by PET-CT. Response evaluation was performed every two cycles during induction therapy. In the maintenance phase, efficacy was evaluated every 3 months until documented disease progression, initiation of a new antineoplastic therapy, loss to follow-up, or death. In patients with suspected PD before the next scheduled tumor evaluation, an unscheduled tumor evaluation was performed. An end-of-treatment visit occurred 4 weeks after the last dose if assessments and examinations were not performed within 7 days before discharge. If subsequent antineoplastic therapy was initiated within this period, the end-of-treatment visit was completed before the initiation of a new antineoplastic therapy.

c. Liver function including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), gamma-glutamyl transpeptidase (GGT), albumin (ALB)

d. Electrolytes include potassium, sodium, chloride, calcium, magnesium."

e. Renal function including: urea nitrogen (BUN), creatinine (Cr).

f. Thyroid function including T3, T4, free T3, free T4 and thyroid stimulating hormone (TSH);

g. Examination results obtained at the same study center within 7 days before informed consent was received. Subjects who were hepatitis B surface antigen-positive and/or hepatitis C surface antigen-positive during the screening phase were tested for HBV DNA and/or HCV RNA on day 1 of each cycle (CxD1) before intravenous administration within a window of ±3 days and within a window of ±7 days during the follow-up phase.

h. Blood pregnancy testing is required only for women of child-bearing age.

i. Includes BNP and cTnI. BNP and cTnI were collected according to the condition of the patients when the treatment was terminated prematurely. Investigators may increase the frequency of measurement as clinically indicated.

j. At baseline, paraffin-embedded biopsy specimens or white slides were available but not required; After disease progression, repeat biopsies were performed to obtain tissue samples when feasible.

k. Peripheral blood samples will be obtained for biomarker studies before treatment and in response to treatment and progression.

1. RESEARCH BACKGROUND

1.1 Current status of treatment of extranodal NK/ T-cell lymphoma

NK/T-cell lymphomas are found almost exclusively in extranodal sites. They are classified as nasal, non-nasal, and disseminated. And lateral nasal type NK/T cell lymphoma (extranodal natural killer/T - cell lymphoma, nasal type, ENKTL), is a mainly happens on the outside of the lymph node non-Hodgkin's lymphoma, mostly in Asia and Latin America, and Europe and the United States is rare [1]. The lesions mainly occur in the upper respiratory and digestive tract, and mainly invade the nasal cavity, paranasal sinuses and other midline facial structures. Patients with advanced disease often present with B symptoms (fever, weight loss, night sweats) and lymphoma-associated hemophagocytic syndrome (lymphoma-associated hemophagocytic syndrome). LAHS) [2, 3]. Occasionally found in non-nasal sites, including the skin, gastrointestinal tract, testes, and salivary glands, it is referred to as non-nasal NK/T-cell lymphoma. In special cases, the lymphoma can spread, involving the skin, lymph nodes, liver, spleen, bone marrow, and peripheral blood. This rare case is disseminated NK/T cell lymphoma.

In the past decade, combination therapy based on asparaginase has greatly improved the survival prognosis of ENKTL patients. The researchers' team pioneered P-GEMOX (pegaspargase, gemcitabine, oxaliplatin) regimen containing pegaspargase for ENKTL, which has ideal efficacy, low toxicity, and easy to use. This regimen has ideal efficacy, low toxicity, and convenient use. The length of hospital stay is significantly shortened, and it is recommended by the NCCN guidelines as the first-line treatment [4]. Further, the researchers' team carried out the national multicenter study, and created the P - GEMOX sequential chemotherapy radiotherapy combined treatment mode, which enabled the CR rate of patients with early ENKTL to reach over 90%, the 5-year OS to reach 80%, and the tolerance was superior to other combined chemoradiotherapy

models [5] (Am J Hematol, 2021, Corresponding author). In order to further improve the efficacy of high-risk patients in the early stage, researchers' team led an international multicenter study of ENKTL, and established a 7-SNP predictive signature for ENKTL. Combined with age, clinical stage and other factors, high-precision prognosis stratification could be achieved. On the basis of model identification of the "high risk" patients death risk was 3.5 times that of the patients with "low risk", and be combined radiation and chemotherapy in patients with high-risk can further improve the long-term survival [6] (Blood, 2021, the corresponding author).

However, even in the era of asparaginase, the prognosis of patients with advanced ENKTL is still poor, with a 5-year OS of less than 30%. New treatment modalities are urgently needed to improve the survival of these patients. Previous studies by researchers found that PD-L1 was highly expressed in tumor tissues and tumor cells of ENKTL, and the level of soluble PD-L1 (sPD-L1) in serum of patients was significantly higher than that of healthy people, which was an important prognostic factor of ENKTL [7]. Based on this, the researchers further developed the immunochemotherapy regimen of PD-1 monoclonal antibody combined with P-GEMOX, which improved the ORR to 88.9% and CR rate to 80% in patients with advanced ENKTL, and the regimen was well tolerated [8] (Signal Transduct Target Ther, 2020, Corresponding author). The efficacy of this new mode of immunochemotherapy has also been verified in a prospective, multicenter phase 2 clinical trial (NCT04127227), and has been included in the Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for lymphoma.

After more than ten years of serial studies, researchers have greatly improved the survival prognosis of patients with early-stage ENKTL, and for the first time, the new immunochemotherapy regimen has been included in the treatment standard of advanced ENKTL. However, we have observed that there are still some patients who will develop drug resistance or relapse in clinical practice, and these patients have a very poor

response to subsequent treatment, with a median OS of 3.6-6.4 months [9-11]. However, there is no standard treatment at present, so there is an urgent need to explore new combination regimens to improve the survival prognosis of these patients.

1.2 Application of PD-1 monoclonal antibody in ENKTL, mechanism of action and clinical efficacy of tislelizumab

The ORR of PD-1 monoclonal antibody monotherapy in the treatment of relapsed and refractory ENKTL was 57%-100%, and the 1-year OS rate was about 80% [12-15]. Further study by the researcher team found that in relapsed and refractory ENKTL patients, PD-1 monoclonal antibody combined with histone deacetylase inhibitor chidamide achieved an ORR of 58.3% and a CR rate of 44.4% [16]. The above study revealed that the combination therapy containing anti-PD-1 monoclonal antibody could further improve the treatment efficacy of relapsed and refractory ENKTL. To improve the long-term survival.

Tislelizumab is the first PD-1 monoclonal antibody to be genetically engineered to modify the FC segment. It binds to PD-1 with high affinity, effectively inhibits PD-1-mediated T cell inactivation, enhances T cell function (in vitro), and inhibits tumor growth. The unique design of the modified Fc segment minimizes the binding of tislelizumab to Fc-γ receptor 1 (Fc-γ R1) on macrophages, thereby avoiding Antibody-dependent cellular phagocytosis (ADCP). It can effectively avoid T cell depletion. In the real world, tislelizumab has good efficacy in the treatment of relapsed and refractory lymphoma, with mild adverse events and controllable safety. At present, tislelizumab has been carried out in phase 2/III clinical trials in a variety of solid tumors, lymphoma and other hematological tumors. A global, multicenter, single-arm, phase 2 study showed that tislelizumab in patients with R/R ENKTL brought the certain efficacy, with the CR rate was 18.2%, the median PFS was 2.7 months, and the 12 months-PFS was 22.7% [17]. These results indicate that tislelizumab has a broad application prospect in

patients with ENKTL.

1.3 Mechanism and clinical efficacy of liposomal mitoxantrone

Mitoxantrone has shown good therapeutic effect in lymphoma. As the most successful drug delivery system, liposomes can reduce the free drug concentration in the blood and minimize systemic toxicity. It can prolong the circulation time of drugs in blood and facilitate the enrichment of mitoxantrone in tumor tissues, so as to improve the therapeutic effect of drugs. The preclinical pharmacodynamic, pharmacokinetic and toxicological studies of liposomal mitoxantrone injection suggest that liposomal mitoxantrone injection has stronger anti-tumor activity. In addition to the new skin toxicity, the main toxicity of liposomal mitoxantrone injection was significantly reduced compared with mitoxantrone. The team led by the multicenter phase 2 clinical research results show that the liposomal mitoxantrones monotherapy for the treatment of recurrence/refractory PTCL ORR was 40.7%, and the CR rate was 20.4%; Among them, the ORR for relapsed/refractory ENKTL was 52.4% (11/21), which ranked the first among all subtypes [18], indicating that liposomal mitoxantrone has a good application prospect in relapsed and refractory ENKTL, and it is necessary to further explore its combination regimen in clinical practice.

1.4 The application of PD-1 monoclonal antibody combined with chemotherapy resistance pattern in lymphoma research

The use of PD-1 monoclonal antibody combined with chemotherapy can destroy the tumor structure, destroy the body's possible immune rejection of the drug, and cause antigen shedding, which can achieve rapid control of the disease. In solid tumors, this approach has shown promising outcomes in non-small cell lung cancer, head and neck squamous cell carcinoma, and other malignancies [19-20]. In the field of lymphoma,

previous studies by researchers found that PD-1 monoclonal antibody combined with GVD regimen chemotherapy could further prolong event-free survival in patients with classical Hodgkin lymphoma [21]. In ENKTL, the combination of P-GemOx chemotherapy with a PD-1 monoclonal antibody was first innovatively introduced by researchers. This immunochemotherapy mode can drive a deeper and durable tumor response, increasing the complete response rate from 56% to 78%, and it is well tolerated [8].

Based on the above research, we propose the following scientific hypothesis: The PD-1 monoclonal antibody of tislelizumab combined with liposomal mitoxantrone can further improve the efficacy and long-term survival of relapsed and refractory ENKTL. Therefore, we plan to conduct the phase 1b/2 clinical study of tislelizumab combined with liposomal mitoxantrone in the treatment of relapsed/refractory ENKTL. The aim of this study is to explore the efficacy and safety of tislelizumab combined with liposomal mitoxantrone in the treatment of relapsed/refractory ENKTL, and to provide more effective treatment options for patients. The mechanism of ENKTL drug resistance was revealed from both basic research and clinical transformation, the genes related to the sensitivity of anti-PD-1 monoclonal antibody combined with liposomal mitoxantrone were screened, and the predictive indicators of immunotherapy sensitivity were constructed, so as to provide a theoretical basis for the establishment of a new treatment plan for ENKTL.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary objectives and endpoints

- Dose-escalation phase

  To evaluate the DLTs of liposomal mitoxantrone combined with tislelizumab, and explore the RP2D.

- Dose-expansion phase

To evaluate the efficacy of tislelizumab combined with liposomal mitoxantrone in relapsed/refractory ENKTL, which is the complete response rate.

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2.2 Secondary objectives and endpoints

- Dose escalation phase

  1. Safety and adverse events (according to NCI CTC AE v5.0);

  2. Laboratory examination; CR rate, objective response rate (ORR), disease control rate [DCR: CR+PR+ stable disease (SD)].

- Dose-expansion phase

  1. ORR, DCR, progression-free survival (PFS) and overall survival (OS).

  2. Safety.

2.3 Exploratory objectives

To explore the correlation between biomarkers and the efficacy of tislelizumab combined with liposomal mitoxantrone treatment.

3. STUDY POPULATION

3.1 Population

Patients with refractory relapsed ENKTL who had failed asparaginase-based chemotherapy or chemoradiotherapy.

3.2 Planned enrollment number

1. Dose-escalation phase: 6 to 12 patients were planned to be enrolled;

2. Dose-expansion phase: A single-stage design method was used to determine the sample size. The null hypothesis assumed a complete response rate of 28% for Lipo-

MIT monotherapy, and an estimated target complete response rate of 50% for patients treated with Lipo-MIT combined with tislelizumab. Therefore, based on an exact binomial test with a one-side α of 0.05 and 80% power, a sample size of 32 patients was required. The null hypothesis would be rejected if at least 14 patients achieved complete response. Allowing for a 10% dropout rate, the planned sample size was 36 patients.

3.3 Inclusion criteria

1. ENKTL confirmed by histopathology at the study center;
2. Willingness to participate in trial; Fully understand and be informed of the study and sign written informed consent;
3. Age of 18-75 years at the time of enrollment;
4. Patients with refractory or relapsed ENKTL who had failed asparaginase-based chemotherapy or chemoradiotherapy. Refractory disease was defined as: i) failure to achieve a complete response after asparaginase-based chemotherapy; or ii) disease progression within 6 months after the last asparaginase-containing regimen; Relapsed disease was defined as recurrence of lymphoma after achieving complete response after initial therapy;
5. Eastern Cooperative Oncology Group performance status of 0-2;
6. Estimated life expectancy ≥3 months;
7. At least one measurable lesion according to the Lugano 2014 criteria;
8. No evidence of hemophagocytic lymphohistiocytosis (HLH). Patients with clinically diagnosed HLH could be enrolled only after receiving therapy for HLH and being assessed by the investigator as clinically stable and suitable for study participation;
9. Adequate organ and bone marrow function, defined as follows:
   a) Bone marrow function: absolute neutrophil count (ANC) ≥ 1.5×10^9/L (≥1.0×10/L for patients with bone marrow involvement), platelet count (PLT) ≥ 75×10^9/L (≥50×10^9/L for patients with bone marrow involvement), and hemoglobin (HGB) ≥ 8.0 g/dL;

No receipt of granulocyte colony-stimulating factor, platelet transfusion, or red blood cell transfusion within 14 days prior to enrollment;

b) Hepatic function: Total bilirubin (TBIL) ≤1.5× upper limit of normal (ULN) (≤3.0×ULN if with liver involvement); alanine aminotransferase (ALT) and aspartate transferase (AST) ≤2.5×ULN (≤5.0×ULN if with liver involvement);

c) Renal function: serum creatinine (Cr) ≤1.5×ULN;

d) Coagulation function: International normalized ratio (INR) ≤1.5 × ULN; Prothrombin time (PT) and activated partial thromboplastin time (APTT) ≤1.5×ULN, unless the patient is receiving anticoagulant therapy and the values fall within the expected therapeutic range;

e) Thyroid function: Thyroid-stimulating hormone (TSH) or free thyroxine (FT4) or free triiodothyronine (FT3) were within the normal range ±10% (note: patients with non–autoimmune thyroid disorders, or those receiving stable replacement therapy with FT3/FT4 within the normal range, were eligible);

3.4 Exclusion criteria

1. Prior treatment with liposomal mitoxantrones, or a cumulative dose of doxorubicin > 360 mg/m^2 or a cumulative dose of mitoxantrone > 160mg/m^2;
2. History of another malignancy within the past 5 years, or concurrent malignancy, with the exception of adequately treated basal cell carcinoma of the skin;
3. Aggressive NK-cell leukemia or central nervous system invasion;
4. Participation in another investigational drug clinical trial within 4 weeks prior to the start of study treatment;
5. Receipt of any anticancer therapy within 4 weeks prior to study treatment initiation;
6. Receipt of allogeneic hematopoietic stem-cell transplantation within 3 years before the administration of the study treatment (patients were eligible if they had undergone allogeneic hematopoietic stem-cell transplantation more than 3 years before the administration of the study drug and did not have current graft-versus-

host reactions); receipt of autologous hematopoietic stem-cell transplantation within 100 days before the administration of the study treatment;

7. Patients with a known history of human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome;
8. Patients with active chronic hepatitis B or active hepatitis C infection. Patients positive for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBc Ab), or hepatitis C antibody (HCV Ab) must undergo further HBV DNA (≤1000 copies/mL or ≤500 IU/mL) and HCV RNA testing (below the lower limit of detection). Patients may be enrolled only after exclusion of active infection. HBV carriers, patients with medically controlled HBV (HBV DNA ≤1000 copies/mL or ≤500 IU/mL), and those with cured HCV infection could be included.
9. Patients who were receiving systemic glucocorticoids or other immunosuppressive therapy within 14 days prior to study treatment (Topical, ophthalmic, intra-articular, intranasal, or inhaled corticosteroids with minimal systemic absorption are permitted. Short-term [≤7 days] corticosteroid use for prophylaxis—e.g., contrast allergy—or for non-autoimmune conditions is allowed.).
10. Active autoimmune disease requiring systemic treatment within the past 2 years (Patients with conditions controlled on replacement therapy only—e.g., type 1 diabetes, hypothyroidism on hormone replacement, or adrenal/pituitary insufficiency on physiological glucocorticoids—could be included);
11. Cardiac dysfunction and disease, including any of the following:

    a) Long QTc syndrome or QTc interval >480 ms;

    b) Complete left bundle branch block, or second- or third-degree atrioventricular block;

    c) Severe, uncontrolled arrhythmias requiring medical treatment;

    d) NYHA class ≥ III heart failure;

    e) Left ventricular ejection fraction (LVEF) < 50%;

f) History of myocardial infarction, unstable angina, clinically significant ventricular arrhythmias or other arrhythmia requiring treatment, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities within 6 months before enrollment;

12. Major surgery within 28 days before enrollment, or presence of unhealed wounds or incompletely healed fractures;
13. Receipt of a live attenuated vaccine within 4 weeks before enrollment or planned during the study (except influenza vaccine);
14. Pregnancy or breastfeeding, or women and men of childbearing potential unwilling to use effective contraception;
15. Psychiatric illness or cognitive impairment that would preclude provision of informed consent;
16. Active infection, except tumor-related fever (B symptoms).

3.5 Withdrawal criteria

1. Voluntary withdrawal of informed consent by the participant requesting discontinuation from the clinical trial.
2. Disease progression confirmed by medical imaging (e.g., CT, MRI, or ultrasonography) or clinical progression as determined by the investigator (the reason for determining progression must be documented in detail).
3. Intolerable toxicity.
4. Completion of 1 year of treatment.
5. Loss to follow-up.
6. Occurrence of pregnancy during the study.
7. Investigator’s decision that withdrawal is necessary (with detailed documentation of the reason).
8. Sponsor’s decision to terminate the study for safety or other special considerations.

4. TREATMENT PLAN

4.1 Treatment regimen

4.1.1 Induction therapy period

Phase 1 Dose-escalation phase of the study

Participants will receive tislelizumab in combination with liposomal mitoxantrone. Tislelizumab will be administered at a fixed dose, whereas the dose of liposomal mitoxantrone will be escalated sequentially from the lower to the higher dose levels. The treatment regimen will be administered once every 4 weeks. The first cycle of treatment will serve as the dose-limiting toxicity (DLT) observation period. Participants who complete the 4-week treatment and observation of cycle 1 may proceed to subsequent cycles, until the occurrence of relapse or progression, death, withdrawal of consent, initiation of alternative therapy, or completion of the study—whichever occurs first. Relevant clinical assessments will be performed throughout the study to evaluate safety and tolerability.

1. Dose-escalation protocol

- In the dose-escalation phase, 16 mg/m^2 of liposomal mitoxantrone was used as the initial dose, and two dose groups of 16 mg/m^2 and 20 mg/m^2 were designed.
- Tislelizumab was given at a fixed dose of 200 mg, q4w.
- Principle of dose-escalation

  (1) Dose escalation followed the “3 + 3” design. Each dose level enrolled 3–6 patients, and safety and tolerability were assessed during the first treatment cycle. If no DLT occurred among the first three patients, the trial proceeded to the next higher dose level as planned. If one DLT occurred, three additional patients were enrolled at the same dose level; escalation continued if no further DLTs were observed. If two or more DLTs occurred at a given

dose level, the preceding dose level was defined as the maximum tolerated dose (MTD).

(2) At least 6 patients were required to complete DLT observation at the MTD dose.

(3) Patients who developed a DLT were managed according to standard clinical practice at the discretion of the investigator. Treatment could be delayed by up to 2 weeks, and patients could resume therapy at the same dose or at a reduced dose level in the subsequent cycle.

(4) If more than one patient experienced a DLT at the lowest prespecified dose (16 mg/m²), the investigator and sponsor could jointly consider exploring a lower dose (12 mg/m²). Conversely, if no MTD was identified at the highest prespecified dose (20 mg/m²), the investigator and sponsor could discuss whether to continue escalation to higher dose levels.

2．Dose-limiting toxicities (DLTs)

DLTs were defined as adverse events considered related to the investigational drug that occurred within the first 28 days after initial administration (Cycle 1, Day 1–28), and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE v5.0). The specific criteria were as follows:

Hematologic toxicities:

(1) Grade 4 neutropenia not recovering to baseline within 7 days;

(2) Grade 4 thrombocytopenia, or grade 4 anemia;

(3) Grade ≥ 3 febrile neutropenia not recovering to baseline within 7 days;

(4) Grade 3 thrombocytopenia associated with bleeding tendency or requiring platelet transfusion.

Cardiac toxicities:

(1) Grade ≥ 3 left ventricular systolic dysfunction;

(2) Grade ≥ 3 heart failure;

(3) Grade ≥ 3 decrease in left ventricular ejection fraction.

Other non-hematologic toxicities:

Any grade ≥ 3 other non-Hematologic toxicity, except the following protocol-defined, manageable conditions:

(1) Transient (≤24 h) grade 3 fever (>40 °C), fatigue, headache, or nausea, recovering to grade ≤1 or baseline after treatment

(2) Grade 3 diarrhea, vomiting, or electrolyte disturbances (including hypokalemia, hypophosphatemia, or hypocalcemia) recovering to grade ≤1 or baseline within 48 hours after treatment;

(3) Grade 3 liver function abnormalities recovering to grade ≤1 or baseline within 2 weeks;

(4) Grade 3 skin reactions (severe rash, hand–foot syndrome, or other cutaneous toxicities) recovering to grade ≤1 or baseline within 2 weeks after appropriate management;

(5) Grade 3 infection secondary to skin lesions;

(6) Grade 3 hypertension recovering to grade ≤2 within 3 days after treatment;

(7) Grade 3 hyperglycemia (in patients with diabetes mellitus or impaired glucose tolerance) that is medically controllable;

(8) Grade 3 anorexia recovering to grade ≤1 or baseline within 7 days after supportive therapy;

(9) Serum albumin ≤ 20 g/L

3. Maximum tolerated dose (MTD)

The MTD was defined as the highest dose level at which no more than 33% of patients experienced a DLT, with at least six patients evaluable for DLT assessment at that dose level.

4. Recommended phase 2 dose (RP2D)

If an MTD of liposomal mitoxantrone hydrochloride was identified, the MTD was selected as the RP2D. If no MTD was reached, the RP2D was

determined jointly by the investigators and the sponsor based on safety data from the DLT observation period during dose escalation. The RP2D was used for enrollment during the dose-expansion phase.

Dose-expansion phase of the study

To explore the efficacy, safety and tolerability of liposomal mitoxantrone combined with tislelizumab at the RP2D dose level.

Tumor assessments were performed every two cycles during induction therapy.

4.1.2. Maintenance therapy period

After completion of six induction cycles, tumor response was assessed. Participants achieving complete response (CR), partial response (PR), or stable disease (SD) proceeded to maintenance therapy.

Tislelizumab was administered at 200 mg on Day 1 every 3 weeks (q3w) and continued until disease progression, unacceptable toxicity, or with a maximum total treatment duration of 12 months, whichever occurred first.

Tumor assessments were conducted every 3 months during the maintenance phase.

4.2 Guidelines for dose modification, interruptions and discontinuation

4.2.1 Dose interruptions and discontinuation for tislelizumab

Tislelizumab dose modification is not permitted throughout the study. The criteria for temporary interruption and permanent discontinuation of tislelizumab are summarized in the table below.

The criteria for interruption and permanent discontinuation for tislelizumab

Immune-related adverse events	Severity *	Adjustment protocol
Pneumonia	Grade 2	Withhold treatment until adverse events resolve to grade 0–1
	Grade 3-4 or recurrent grade 2	Permanent discontinuation
Diarrhea or colitis	Grade 2-3	Withhold treatment until adverse events resolve to grade 0–1
	Grade 4	Permanent discontinuation
Hepatitis	Grade 2, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in 3 to 5 times the upper limit of normal (ULN) or total bilirubin in 1.5-3 x ULN	Withhold treatment until adverse events resolve to grade 0–1
	Grade 3-4, AST and ALT > 5 x ULN, or total bilirubin > 3 x ULN	Permanent discontinuation
Nephritis	Grade 2-3 elevated serum creatinine	Withhold treatment until adverse events resolve to grade 0–1
	Elevated serum creatinine grade 4	Permanent discontinuation
Endocrine disorders	Symptomatic grade 2-3 hypothyroidism, grade 2-3 hyperthyroidism, grade 2-3 hypophysitis, and grade 2 adrenal insufficiency Grade 3 hyperglycemia or type 1 diabetes	Withhold treatment until adverse events resolve to grade 0–1
	Grade 4 hypothyroidism Grade 4 thyroid function hyperfunction 4 the pituitary gland inflammation Grade 3-4 adrenal insufficiency Grade 4 hyperglycemia or type I diabetes	Permanent discontinuation

	mellitus	
Adverse skin reactions	Grade 3, or suspected Stevens Johnson syndrome (Stevens - Johnson syndrome, SJS) or Toxic Epidermal necrosis loose solution (Toxic Epidermal Necrolysis, TEN)	Administration was withheld until symptoms resolved or returned to baseline and corticosteroid ≤10 mg/ day (cannot be restarted until SJS/TEN has been ruled out).
	Grade 4 rash, or confirm SJS and TEN	Permanent discontinuation
thrombocytopenia	Grade 3 or 4	Withhold treatment until adverse events resolve to grade 0–1
Other	Grade 3-4 higher blood amylase and lipase increased Grade 2-3 pancreatitis Grade 2 myocarditis [a] Grade 2 encephalitis Grade 2-3 other correlation immune reactions occur for the first time	Withhold treatment until adverse events resolve to grade 0–1
	Grade 4 or recurrent pancreatitis of any grade Grade 3-4 myocarditis Grade 3-4 encephalitis Grade 4 Other immune-related adverse events occurring for the first time	Permanent discontinuation
Recurrent or persistent adverse events	Recurrent grade 3-4 (excluding endocrine disease) The last 12 weeks after the treatment grade 2-3 did not improve to Grade 0-1 (except for endocrine disease) The last 12 weeks after the treatment corticosteroid failed to fall to the equivalent dose	Permanent discontinuation

	of 10 mg/day or less prednisone	
Infusion reactions	Grade 2	Reduce the dripping speed, or pause when symptoms can resume after drug use and close observation
	Grade 3-4	The product must be stopped immediately and permanently and treated appropriately

a. The safety of restarting treatment with this drug after treatment of myocarditis to grade 0-1 is unknown

4.2.2 Dose modification, interruptions and discontinuation for liposomal mitoxantrones

The adverse events should be closely monitored during the use of this product and adjusted according to the adverse events so that the patient can tolerate the treatment. The adverse events caused by this product can be treated by symptomatic treatment, drug suspension and or dose adjustment. Patients were treated with RP2D as the initial dose, and the dose was reduced according to the principle of dose adjustment. The initial and subsequent dose reduction levels were 20, 16, and 12 mg/m^2 (for example, RP2D was $20mg/m^2$).

Investigators should adjust doses in the following manner, depending on the degree of adverse effects:

Adverse events	**Dose adjustments**
Grade 4 non-hematologic adverse events	• Occur for the first time: follow-up period required by the doctor according to the clinical risk benefit ratio to determine whether patients treated with this product, if continue to treatment, dose should

	be down to the next dose level • Happening again grade 3 and above non hematologic adverse events, should terminate this treatment
Grade 4 hematological adverse events Grade 3 non-hematologic adverse events	• First occurrence: dose reduction to the next dose level in subsequent cycles • Second occurrence: dose reduction by another dose level in subsequent cycles • Third occurrence: discontinuation of the drug
Grade 3 hematological adverse events	• First occurrence: the original dose could be maintained in subsequent cycles • Second occurrence: dose reduction to the next dose level in subsequent cycles • Third occurrence: dose reduction by another dose level in subsequent cycles • Fourth: termination of treatment

4.3 Concomitant therapy

4.3.1 Prohibited therapy

The use of CFDA-approved anticancer agents is prohibited during the trial, including chemotherapeutic drugs, modern Chinese herbal preparations, and immunomodulatory agents (such as thymosin, interferon, interleukin-2, and lentinan).

4.3.2 Cautious therapy

Systemic corticosteroids and other immunosuppressive agents: They may interfere with the pharmacodynamic activity of tislelizumab. However, systemic corticosteroids and other immunosuppressants may be used after treatment initiation if required for the

management of immune-related adverse events. Corticosteroids may also be administered as prophylaxis to prevent chemotherapy-related adverse reactions.

4.3.3 Permitted therapy

1. Participants can support therapy. Support treatment can be combined with the following drugs or related treatment: antibiotics, analgesic, psychological treatment, such as any other used to provide the best support necessary to symptomatic treatment. For other research or antitumor drugs to chemical/endocrine, immune therapy, is beyond the scope of defined support treatment.
2. If the researchers think that has no effect on the end, allowing the unconventional treatment (such as herbal medicine or acupuncture) and vitamin/mineral supplementation. During treatment the patients could double phosphonic acid salt treated bone destruction.
3. During treatment, if the clinical manifestations of tip or according to the needs of researchers determine the treatment of acute toxic effects such as neutrophils, reduce fever can use granulocyte colony stimulating factor and other hematopoietic growth factors. Long-term use of erythropoietin was permitted.

4.4 Adverse events and management

4.4.1 Tislelizumab-related adverse events and management

1) Adverse events related to tislelizumab

Hypothyroidism, fatigue, elevated ALT, AST, elevated, skin rashes, anemia, and pulmonary infection

2) Immune-related adverse events caused by tislelizumab

Level correlation immune associated pneumonia, diarrhea colitis, correlation immune

correlation of hepatitis, nephritis, correlation immune endocrine disease (hypothyroidism and thyroid function hyperfunction, other thyroid diseases, the pituitary gland inflammation, adrenal insufficiency, hyperglycemia, and type 1 diabetes), correlation immune skin adverse events, immune related myocarditis, correlation of pancreas Gland inflammation, immune thrombocytopenia correlation, correlation immune nervous system adverse reaction, transfusion reaction, etc.

3) Management of immune-related adverse events

In principle, according to the severity of adverse events, refer to the adjustment principle of tislelizumab 4.2.1. Management of immune-related adverse effects should be in accordance with the medical practice and guidelines of the study institution.

4.4.2 Liposomal mitoxantrone-related adverse events and management

1) Hematological adverse events

Mitoxantrone hydrochloride is a cell cycle-specific chemotherapeutic drug. Hematologic toxicity is a very common adverse reaction of chemotherapy drugs.

Hematological adverse events should be closely monitored during treatment. If cytopenia occurs, symptomatic treatment should be given according to clinical needs, and the dose should be reduced in the subsequent treatment cycle if necessary.

2) Cardiac adverse events

Cardiotoxicity is an adverse effect of anthracyclines that needs special attention, and most of it occurs within the first year of treatment. According to the time of occurrence of toxicity, it can be divided into acute, chronic and delayed. Acute toxicity mainly occurs a few hours or a few days after medication, mainly with myocardial injury. Clinically, ECG abnormalities (arrhythmia, ischemic changes, etc.) and elevated cardiac damage markers

are common. Chronic and delayed cases are mainly characterized by decreased left ventricular ejection fraction (LVEF), which can be clinically manifested as only subclinical echocardiographic changes, and may also have symptoms related to congestive heart failure.

Cardiac function should be monitored in patients treated with this drug. Once cardiac adverse events occur, they should be actively treated and the therapeutic dose should be adjusted. If necessary, a cardiologist should be consulted to evaluate the risks and benefits together before deciding whether to continue the medication. In case of left ventricular ejection fraction (LVEF) reduce cardiac adverse events, according to the principle of the table below for processing.

Severity of cardiac adverse events	**Dose adjustment**
EF of 50 to 40% or a 10-19% decrease from baseline or grade 2 heart failure	• Only when treatment benefit more than potential risks, can continue to use this product for treatment
EF < 40% or > 20% decrease from baseline or heart failure grade ≥3	• Discontinued, safeguarding the heart function treatment
• Once symptoms of heart failure patients, recommended to the corresponding guidelines for cardiac function maintenance treatment • If myocardial enzymes are elevated during the treatment, enalapril treatment is recommended for 1 year, and echocardiography should be repeated at least every 3 months for 1 year after the end of the treatment.	

3) Infusion-related reactions

Infusion-related reactions typically occur within 5-30 minutes after administration, most often during the first infusion, although occasional cases have been reported in subsequent cycles. Clinical manifestations may include flushing, dyspnea, facial swelling, headache, chills, chest pain, back pain, a sense of chest or throat tightness, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension.

Severity of infusion-related reactions	**Principles of management**
Grade 2-3	• Reduce the infusion rate or suspend the infusion • Symptomatic and supportive treatment, choose different physical/drug treatment methods, such as low fever, physical cooling by bath and other means; Antipyretic and analgesic drugs can be given at high temperature. Giving glucocorticoid or antihistamines to reduce allergic reaction and so on
Grade 4	• Stop the medication immediately and take active rescue treatment

4) Infection

Some patients receiving treatment developed infections, most commonly upper respiratory tract infections and infectious pneumonia. Severe infections may be fatal.

Patients with severe infections prior to treatment should begin study therapy **o**nly after the infection is adequately controlled. During treatment,

patients should be closely monitored for fever and other signs or symptoms of infection, and appropriate management should be provided when infection is suspected.

5) Hepatic impairment

Because hepatic dysfunction may reduce the metabolism of mitoxantrone, patients with impaired liver function should be monitored closely during treatment. Should hepatic injury occur, hepatoprotective therapy should be initiated promptly, and liver function should be monitored weekly until it returns to baseline. Dose adjustment may be required in subsequent treatment cycles.

6) Interstitial pneumonitis

During treatment, patients should be monitored carefully for symptoms such as fever, cough, and dyspnea. If new or worsening respiratory symptoms (e.g., tachypnoea or breathlessness) occur and interstitial lung disease is suspected, a chest X-ray or other appropriate imaging should be performed without delay. Treatment should be discontinued, and corticosteroids and other supportive measures should be administered as clinically indicated.

5. PROCEDURE OF THE STUDY

Participants must read and sign the informed consent form approved by the Ethics Committee (EC). All assessments and study procedures shall be performed according to the schedule outlined in the study flow chart. Variations within the permitted visit windows are allowed to accommodate holidays, weekends, or logistical considerations.

5.1 Assessments during screening period

Screening period since signing informed consent, and began to study medicine or screening fail over. The patients must be specified in the signed written informed

consent for this study of the screening process. Before signing informed by clinical routine nursing laboratory examination and radiographic assessment of the need to do, if the specified window period, relevant data can be used.

Unless specified, the following screening was completed no later than 28 days before the initiation of the study drug.

- ✓ Signed informed consent;
- ✓ Demographic information: gender, height, weight, date of birth;
- ✓ Smoking history, history of allergies;
- ✓ Basic diseases and the diagnosis and treatment;
- ✓ The diagnosis of tumor cancer diagnosis: including the date. At baseline, paraffin-embedded biopsy tissue samples or white patches may be retained under certain conditions, but it is not mandatory. Before treatment, peripheral blood samples will be collected for biomarker research;
- ✓ Imaging included PET-CT or contrast-enhanced CT and/or MRI (nasopharynx, neck, chest, upper and lower abdomen, pelvis), and brain MRI when brain metastases were suspected (CT could be used instead if MRI was contraindicated). As long as there is a measurable/measurable lesion, it can be used for screening tumor assessment, and the non-measurable lesion can be evaluated by PET-CT;
- ✓ History of cancer;
- ✓ Virological examination: HBs Ag (if positive, HBV-DNA), HBs Ab, HBeAg, HBeAb, HBc Ab, HCV-Ab (if positive, HCV-RNA), HIV-Ab, EBV-DNA;

The following screen should be completed within 7 days before you start study drug, pregnancy test should be completed within 72 h before starting to study drug.

- ✓ ECOG score;
- ✓ Vital signs: pulse, breathing rate, body temperature, blood pressure;
- ✓ Comprehensive physical examination: general situation, face, skin, lymph

nodes, neck, eye, ear, mouth, respiratory system, cardiovascular system, abdomen, reproductive urinary system, musculoskeletal, nervous system, mental state, other;

- ✓ Routine blood, red blood cell count, hemoglobin, platelet count, white blood cell count, neutrophil count, lymphocyte count;
- ✓ Blood biochemical: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, blood urea nitrogen and urea (optimal blood urea nitrogen), total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, Cl^-;
- ✓ Thyroid function: TSH, FT3, FT4;
- ✓ Routine urine: white blood cells, red blood cells and urine protein. If the urine protein ≥ 2+, please check for 24 h urine protein quantitative determination;
- ✓ Blood coagulation function: APTT and PT, FIB, INR;
- ✓ The pregnancy test, serum or urine (applicable to childbearing age women);
- ✓ Echocardiography, 12-lead electrocardiogram, and myocardial injury markers: if abnormal, other necessary tests should be performed according to the investigator's judgment;
- ✓ Drug combination, adverse events: the recording of adverse events since signed informed consent;
- ✓ NYHA cardiac function classification.

5.2 Enrollment

- ✓ Confirm the inclusion criteria;
- ✓ The patients were administered.

5.3 Assessments during treatment period

Each cycle before each drug should complete the following assessment, if the screening period after the first drug delivery within 7 days before detection, drug delivery for the first time do not need to test again.

- ✓ ECOG score;
- ✓ Vital signs: pulse, breathing rate, body temperature, blood pressure;
- ✓ Comprehensive physical examination: general condition, head and face, skin, lymph nodes, neck, eyes, ear, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, nervous system, mental status, others;
- ✓ Routine blood, red blood cell count, hemoglobin, platelet count, white blood cell count, neutrophil count, lymphocyte count;
- ✓ Blood biochemical: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, blood urea nitrogen and urea (optimal blood urea nitrogen), creatinine, total protein, albumin, blood sugar, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, Cl^-;
- ✓ Thyroid function: TSH, FT3, FT4;
- ✓ Routine urine: white blood cells, red blood cells and urine protein. If the urine protein ≥ 2+, please check for 24 h urine protein quantitative determination;
- ✓ Blood coagulation function: APTT and PT, FIB, INR;
- ✓ Virology inspection: if the screening phase of HBsAg positive, if need to detect HBV DNA, screening HCV - Ab positive, will be expected to detect HCV - RNA.
- ✓ Echocardiography, 12-lead electrocardiogram, and myocardial damage markers: if abnormal, other necessary tests should be performed according to the investigator's judgment;
- ✓ Drug combination, adverse events: the recording of adverse events since signed informed consent;
- ✓ NYHA heart function classification;
- ✓ Patients were carried out in accordance with the established time imaging evaluation, until radiographic progression, and start a new anti-tumor treatment, withdraw the informed consent, death or the end of the study (before). Imaging studies including PET/CT enhancement CT and/or MRI (nose pharynx ministry, neck, chest, upper and lower abdomen and pelvis),

brain metastasis is suspected to do brain MRI (magnetic resonance imaging (MRI) is disabled, CT can substitute for), evaluation measure lesions could not need a PET/CT for review. Every two cycle time during induction therapy efficacy evaluation. Maintenance treatment period efficacy evaluation every 3 months, until the record confirmed disease progression, start a new antineoplastic therapy, lost to follow-up or death. Before the start of the next tumor assessment in the planning of the suspect in PD patients, should be evaluated for an unplanned tumor.

5.4 Assessments during follow-up period

An end-of-treatment visit occurred 4 weeks after the last dose. Follow-up was planned every 3 months during the first 2 years, every 6 months during years 3 to 5, and yearly thereafter.

5.5 Termination of study visits

An end-of-treatment visit occurred 4 weeks after the last dose if assessments and examinations were not performed within 7 days before discharge. If subsequent antineoplastic therapy was initiated within this period, the end-of-treatment visit was completed before the initiation of a new antineoplastic therapy. This should be done as described below:

- ✓ ECOG score;
- ✓ Vital signs: pulse, respiratory rate, temperature, blood pressure;
- ✓ Comprehensive physical examination: general situation, face, skin, lymph nodes, neck, eye, ear, mouth, respiratory system, cardiovascular system, abdomen, reproductive urinary system, musculoskeletal, nervous system, mental state, other;
- ✓ Routine blood, red blood cell count, hemoglobin, platelet count, white blood cell count, neutrophil count, lymphocyte count;
- ✓ Blood biochemical: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP,

blood urea nitrogen and urea (optimal blood urea nitrogen), creatinine, total protein, albumin, blood sugar, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, Cl^-;

- ✓ Thyroid function: TSH, FT3, FT4;
- ✓ Urine routine: white blood cell, red blood cell, urine protein. If the urine protein ⩾ 2+, please check for 24 h urine protein quantitative determination;
- ✓ Blood coagulation function: APTT and PT, FIB, INR;
- ✓ Virological examination: if HBsAg is positive in the screening period, HBV-DNA should be detected, and if HCV-Ab is positive in the screening period, HCV-RNA should be detected.
- ✓ Echocardiography, 12-lead electrocardiogram, and myocardial damage markers: if abnormal, other necessary tests should be performed according to the investigator's judgment.
- ✓ Drug combination, adverse events: the recording of adverse events since signed informed consent.
- ✓ NYHA cardiac function classification
- ✓ Imaging studies including PET/CT enhancement CT and/or MRI (nose pharynx ministry, neck, chest, upper and lower abdomen and pelvis), brain metastasis is suspected to do brain MRI (magnetic resonance imaging (MRI) is disabled, CT can substitute for), evaluation measure lesions could not need a PET/CT for review.

5.6 Off-site visit

During the course of the trial and up to 90 days after the last dose or before starting a new antineoplastic therapy within 90 days after the last dose, patients should record the following items for unscheduled follow-up due to an AE:

- ✓ Concomitant medications;
- ✓ Adverse events;
- ✓ Any relevant tests performed (including imaging, if available).

6. EFFICACY EVALUATION

6.1 Efficacy evaluation criteria

Tumor response was assessed by investigator according to the Lugano 2014 criteria.

6.2 Efficacy and definition

6.2.1 Efficacy

Efficacy parameters mainly included the complete response (CR) rate, partial response rate (PR), objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS), duration of response (DoR).

6.2.2 Definition of efficacy

Complete response (CR) rate is defined as the proportion of patients who achieve complete response with the best response.

Partial response (PR) rate is defined as the proportion of patients who achieve a partial response to the best overall response.

Objective response rate (ORR) is defined as the proportion of patients who achieved CR or PR.

Disease control rate (DCR) is defined as proportion of patients with best overall response of CR, PR or stable disease (SD).

Progression-free survival (PFS) is defined as the date from treatment initiation to first documented disease progression or death, whichever occurred first.

Overall survival (OS) is defined as the time from treatment initiation to death from any cause.

Duration of the response (DoR) is defined as the time from first response to first documented disease progression or death, whichever occurred first.

6.3 Efficacy evaluation method

The efficacy evaluation primarily utilizes imaging modalities including PET-CT or contrast-enhanced CT and/or MRI (nasopharynx, neck, chest, upper/lower abdomen, pelvis). When brain metastases are suspected, a brain MRI should be performed (alternative CT may be used in cases where MRI is contraindicated). Tumor response was assessed by investigator according to the Lugano 2014 criteria.

7. SAFETY EVALUATION

NCI CTCAE v5.0 was used for safety assessment. Researchers are responsible for monitoring safe to enter all the patients of this study, record any adverse events (AE) and the serious adverse event (SAE).

7.1 Adverse events

An adverse event is an adverse medical event that occurs after a subject has received a trial drug, and this event is not necessarily causally related to the treatment. It contains any adverse symptoms, physical signs and diseases, has something to do with medicine on time, but not necessarily associated with medication (always exist condition deteriorated in the process of research also considered adverse events). According to the requirements of GCP, whether or not to test drug constitute a causal relationship, the researchers shall be truthfully recorded in the original record all the adverse events, and copy to case report form (CRF).

7.2 Serious adverse events

Any serious adverse events are in the experimental drug doses, or at any time during the period of observation, in one of the following adverse events:

- Death: within 30 days after accepting a drug to death, or due to the delay of experimental drug toxicity in 30 days after death (as a result of disease progression, has nothing to do with the experimental drug except death);

- Severe life-threatening toxicity requiring hospitalization or prolonged hospitalization;
- Leading to permanent disability or functional impairment;
- Secondary tumor;
- Lead to congenital malformation, or birth defects;
- Other major medical events.

7.3 Management of adverse events

7.3.1 Adverse events

Mild adverse events occurred in patients with only symptoms, but could be tolerated without symptomatic treatment and drug withdrawal. When symptoms affect normal life, the patient unbearable or withdrawal, delayed chemotherapy or symptomatic treatment.

7.3.2 Serious adverse events

In the event of a serious adverse event, study treatment must be discontinued immediately and prompt emergency management provided.

7.4 Event record

During the study period of adverse events must be recorded on the CRF, within 30 days after the last medication if adverse events related to study drug use, also must be recorded on the CRF. For event record should include: description, event time, end time, the extent and frequency, whether to need treatment (if necessary, shall be recorded for treatment), the researchers determine whether adverse events related to test drug.

Incidents should be followed until resolution. Medical documentation of any adverse event should be documented in source documentation (including the report of test results). Such as participants stopped taking due to test end or discharge of the researcher's treatment, the researchers should be the patients of cases in treatment (including arranging and adverse events whether need to continue to follow-up

instructions, etc.) to the doctor to responsible for treatment. This information should be recorded in the original file.

7.5 Reporting of serious adverse events

In the event of a serious adverse event during the trial, the institution undertaking the clinical study must take immediate measures to protect the safety of the patients and immediately verbally report it to the administrative authorities and the sponsor. The incident report in written form within 24 hours of the principal investigator, and ethics committee. Researchers to record the occurrence of serious adverse events in the report time, duration, and the measures and outcome, signed and dated.

8. QUALITY CONTROL, QUALITY ASSURANCE, AND STUDY DOCUMENTATION

8.1 Quality Control

(1) The laboratory quality control measures

All the laboratories in the participating hospitals should establish unified laboratory test indicators, standard operating procedures and quality control procedures.

(2) Requirements of the participants

Corresponding professional expertise, qualifications and scientific research ability. It is determined after qualification review, and the personnel are relatively fixed.

(3) Volunteers personnel training

Through training before clinical trials and research personnel for clinical trial scheme and its various target specific connotation, disable all criteria (e.g., research purpose, drugs, etc.) to fully understand and know.

According to provisions of solution for the objective indicators shall be stipulated in the time, place and method of inspection.

Observe and follow up for adverse events or unanticipated toxic side effects. Subjective symptoms should be described objectively and should not be induced or prompted.

The case report form should be timely, true and accurate to ensure that all conclusions in the clinical trial are derived from the original data.

Blood samples were stored and transported according to standard operating procedures.

(4) Measures to ensure compliance of patients

The doctors should patiently explain to the patients so that they can fully understand and cooperate with the experiment.

(5) Other

Told the patients test drug adverse events that may occur, and in the event of adverse events, shall be immediately call a doctor or hospital.

8.2 Quality assurance

To ensure the quality of testing, before the formal test, the researchers develop a plan of clinical research. The center for the study of management research, must, in accordance with standard operating procedures including accept, storage, distribution and recycling. Study medication may not be used for this clinical trial participants, must ensure that the drug is used only for this clinical trial patients.

The coordinating committee composed of the principal investigator and the heads of each participating unit was responsible for the conduct of the whole trial and the study and solution of the trial related problems.

The investigator shall appoint trial monitors to ensure that participants' rights and welfare are protected throughout the clinical study, that the data recorded and reported

are accurate, truthful, and complete, and that the study is conducted in accordance with the approved protocol, Good Clinical Practice (GCP) guidelines, and all applicable regulatory requirements.

8.3 Management of study drugs

The pharmaceutical companies are responsible for the appropriate packaging and labelling of the investigational medicinal product, indicating that it is for clinical trial use only, as well as for its shipment and delivery. At the clinical trial site, a designated pharmacist or responsible personnel shall receive and store the investigational product. The use of the investigational product is the responsibility of the investigator, who must ensure that all trial medication is used exclusively for participants enrolled in this study, and that dosing and administration strictly follow the protocol. The investigator shall obtain the investigational product on each treatment day, and the site pharmacist or responsible personnel must maintain detailed records, including the investigator's signature and date. If additional medication is required or if unused medication needs to be returned due to changes in enrollment numbers, this must be documented thoroughly.

Study the use of medication record and the number of actual test drugs should be consistent. All of the inconsistent shall verify or explanations. Test research unit should be remaining after the drug is returned to the fund unit, and record return amount, research the usage of drugs, signing date and sign.

Study institution shall establish internal quality assurance system, strict quality supervision and control of the center. Center should be clear the veracity and reliability of laboratory results, unified abnormal value judgment standard. Test related laboratory testing data should be timely and truthfully recorded in the CRF, and shall present the original report or the copy and paste on the medical records. Of abnormal data are required to verify, by the related researchers to do the necessary instructions, tracking and follow-up as needed to the normal or stability.

8.4 Trial Records

All the test data are recorded on the case report form (CRF). It is the investigator's responsibility to record the trial data on the CRF in a timely, accurate, complete, true, and lawful manner. Authors to send the arbitrator to confirm all the data record and report complete, correct all CRF, correct and consistent with the original data. All errors or omissions have been corrected or indicate, signature and dated by the researchers.

8.4.1 Original records

Original records can confirm the real existence of patients and the integrity and authenticity of data. All data recorded on the CRF are derived from the original records and should be consistent with the original records. If data do not agree with the original record of CRF, need according to the original records, modified, or can offer reasonable explanation. Original records were stored at each trial site. Original records including but not limited to the following files:

Laboratory test reports from this center;

Other medical examination records and clinical documentation of the patient;

Patient's discharge summaries.

8.4.2 Review of original data and documents

Associated with this test in addition to the researchers, DMSC, ethics committee personnel as well as drug administration relevant management personnel shall be entitled to refer to the test of the raw data and documents. Investigators should provide complete data upon request for access to trial documents.

8.4.3 Retention of records

Investigators must maintain source data (usually in the patient's chart) for each patient, including a signed informed consent with trial number and trial name, laboratory data,

electrocardiograms, and the like, for information that appears on the case-report form.

The responsible unit for the clinical trial shall retain essential documents for the period required by national regulations (typically for five years after trial completion). After this time, the investigator/institution is no longer required to maintain trial-related records. Basic information including: 1) the ethics committee for approval documents of the revised test solutions and all; 2) All original data; 3) Case report Form (CRF); 4) written informed consent; 5) any other trial related documents.

8.5 Protocol violation

Investigators or sub-investigators must thoroughly document any protocol deviations occurring during the trial and report them to the principal investigator at this center, the ethics committee, and the sponsor. The report should specify whether the deviation was undertaken to prevent potential harm to the patient or was necessitated by unavoidable medical reasons.

9. DATA STATISTICS AND ANALYSIS

9.1 Overall Arrangement

For the single arm design, this study is given priority to with descriptive statistical analysis, application of SPSS 24.0 statistical processing.

9.2 Analysis set

The analysis population included the full analysis set, per-protocol set and safety analysis set. The total number of patients enrolled, the number of patients in each set and the number of patients excluded were recorded to describe the dropout of the trial cases.

Full Analysis Set (FAS): The FAS is defined according to the intention-to-treat (ITT)

principle, excluding only those exceptional cases in which a participant did not receive any study medication or had a major violation of the inclusion or exclusion criteria. All enrolled patients who received at least one dose of study medication are included in the FAS for efficacy analyses.

Per-Protocol Set (PPS): The PPS is derived from the FAS by further excluding all participants with major protocol deviations. This set includes patients who completed at least two treatment cycles, adhered to the study protocol, maintained good compliance, did not use prohibited medications during the study, and completed all required sections of the case report form. No imputation will be performed for missing data. Efficacy analyses will be conducted based on both the FAS and PPS.

Safety Analysis Set (SAS): The SAS includes all patients who received at least one dose of study medication and had at least one post-treatment safety assessment. Participants who were enrolled but never received the study drug or had no safety data will be excluded. This set will be used for all safety analyses.

10. STUDY SCHEDULE

Anticipated date for first patient enrollment: May 2022;

Anticipated completion of enrollment: November 2024;

Anticipated end date of follow-up: November 2025.

11. ETHICAL PRINCIPLES

11.1 Responsibilities of the investigator

The investigators were responsible for ensuring that the clinical study was conducted in accordance with the protocol, current ICH-GCP, and relevant regulations of the State Food and Drug Administration (SFDA) of China.

11.2 Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

During the study, the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines issued by the China Food and Drug Administration (CFDA) must be strictly followed, and all procedures must be conducted in accordance with the requirements of this protocol. Before initiation of the clinical trial, the study protocol, the informed consent form, and all other documents provided to participants must be reviewed and approved by the Institutional Ethics Committee (IEC) of the study site.

11.3 Informed consent

Each participant (or his/her legal representative) must give written consent after being fully informed of the purpose and content of the study, which must be signed (signed and dated) before any trial related procedure is performed. Informed consent should be in accordance with the provisions of the Declaration of Helsinki, current GCP guidelines, and applicable regulations.

Prior to enrollment of potential patients, the investigator or his or her authorized personnel should explain to them the purpose, methods, possible benefits, potential risks, and any possible discomfort associated with the study. Subjects should be informed that participation in the trial is voluntary and that they may withdraw at any time. Whether or not the subject chooses to participate in the study will not have any effect on his (or her) treatment for the disease. If a subject refuses to participate in the study, other treatments will still be available, and this refusal will have no effect on his or her future treatment. Finally, participants should understand that the investigators will keep records of their identities for long-term follow-up if needed and that such records may be accessed by drug administration personnel and investigators to the extent permitted by relevant laws and regulations. The privacy of the patients will be protected. By signing an informed consent form, the subject authorizes the above actions.

Subjects (or their legal representative) should have sufficient time to read the informed consent form and ask questions. Participants (or their legal representative) should sign the informed consent form with their name and date for record after explanation by the investigator and before enrollment. After signing the informed consent form, the subject should obtain a copy of the informed consent form.

If the subject (or his/her legal representative) is unable to read and write, an impartial witness should participate in the entire process of informed consent (including reading and interpreting all written information) and personally sign the name and date after the subject (or his/her legal representative) has given his/her oral consent.

Subjects unable to understand informed consent may participate in the trial only if their legal representative has given informed consent.

If it is not possible to obtain prior consent from the patients and their legal representative is not present at the time, the procedures for enrolling such patients should be clearly described in the protocol, and the consent of the IEC and any recommendations made to protect the rights and health of the patients should be recorded. In addition, the legal representative of the subject should be notified as soon as possible and their consent should be obtained.

11.4 Confidentiality of data

Confidentiality of patients' information shall be strictly enforced by the investigators and participants in the study. The study protocol, documentation, data and all other information thus generated will be kept strictly confidential. All relevant research or data information will not be disclosed to any unauthorized third party without the prior written approval of the research unit. Researchers of other authorized representative, the IRB or regulators provide study medicine pharmaceutical company representatives, researchers can check all the requirements to maintain files and records, including but not limited to: medical records and the patients' medical records. The study site should allow access to these records. The subject's contact information will be securely stored

at the study site for internal use only during the study. For statistical analysis and scientific reports were collected research data, will be uploaded and stored in Sun Yat-sen University Cancer Center. This should not include the subject's contact information or identifying information. At the end of the study, all identifying information from the study database will be removed and archived at the Sun Yat-sen University Cancer Center.

12. DATA PRESERVATION AND SUMMARY

Investigators must maintain source data (usually in the patient's chart) for each patient, including a signed informed consent form with trial number and trial name, laboratory data, and electrocardiograms.

The responsible unit of the clinical trial should keep the basic data of the trial patients for a sufficient period of time (usually 5 years after the end of the trial) according to the national regulations. Basic data includes 1) ethics committee approval documents for test solution and all solutions of the revised; 2) all original data; 3) Case report Form (CRF); 4) written informed consent; 5) any other trial related documents.

13. RESPONSIBILITIES OF EACH PARTY AND PROVISIONS FOR PUBLICATION OF THE PAPER

Various clinical trials unit after test summary, has obtained the consent of the unit project leader, can be published, to participate in academic conferences at home and abroad; When publishing the paper, it should be clearly stated in the appropriate part of the paper: the research and development unit, production unit, clinical research group leader unit; Clinical research papers that have won awards belong to the clinical trial

unit. When papers related to treatment and treatment technology are applied for the medical achievement award, the clinical trial unit should consult with the drug development unit, production unit and clinical research group leader unit and jointly declare.

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Protocol amendments

Versions	Date	Original content	Amendment(s)	Reason(s)
V 1.0	2022-3-21	—	—	—
V 1.1	2023-10-12	extranodal NK/T-cell lymphoma, nasal type	extranodal NK/T-cell lymphoma	The terminology has been revised in accordance with “The 5th edition of the WHO Classification of Haematolymphoid Tumors”.
		SCHEDULE OF ASSESSMENTS FACT-H&N Version 4	Deleted: “FACT-H&N Version 4”	The FACT-H&N was primarily developed for patients with head and neck squamous cell carcinoma and was not fully applicable to patients with systemic NK/T-cell lymphoma.
V 1.2	2025-2-10	Primary endpoints •Dose-expansion phase To evaluate the efficacy of tislelizumab combined with liposomal mitoxantrone in relapsed/refractory ENKTL, which is the objective response rate.	Primary endpoints •Dose-expansion phase To evaluate the efficacy of tislelizumab combined with liposomal mitoxantrone in relapsed/refractory ENKTL, which is the complete response rate.	The sample size calculation was based solely on the complete response rate, which served as the predefined efficacy benchmark of the trial. To maintain consistency between the statistical framework and the endpoint structure, the complete response rate was formally defined as the primary efficacy endpoint
		Anticipated date for first patient	Anticipated date for first patient	Updated based on the study enrollment

		enrollment: May 2022; Anticipated completion of enrollment: January 2024; Anticipated end date of follow-up: January 2025.	enrollment: May 2022; Anticipated completion of enrollment: November 2024; Anticipated end date of follow-up: November 2025.	progress and anticipated follow-up schedule.