CLINICAL STUDY PROTOCOL

Protocol Version No. and Date: V2.0, November 14, 2019
Study Title: Phase I Study of Pegylated Liposomal Doxorubicin (Duomeisu®) Combined with Cyclophosphamide and Vincristine in Pediatric Patients with Relapsed/Refractory Solid Tumor
Clinical Phase: Phase I
Principal Investigators: Prof. Yizhuo Zhang and Prof. Xiaofei Sun
Study Site: Sun Yat-sen University Cancer Center

INVESTIGATOR'S AGREEMENT

I have read the protocol of the study mentioned below,

Study No: CSPC-DMS-PO-01

Study Title: Phase I Study of Pegylated Liposomal Doxorubicin (Duomeisu®) Combined with Cyclophosphamide and Vincristine in Pediatric Patients with Relapsed/Refractory Solid Tumor

Protocol Date and Version No: November 14, 2019, V2.0

and have received the following documents:

▫ Investigator's Brochure (IB)

▫ ICH-GCP

I have read the study protocol and agree that it contains all the information necessary for the conduct of the study. I agree to conduct the study according to the protocol.

I will ensure that all persons assisting with the conduct of the study are adequately informed about the protocol, any protocol amendments, study treatments, and their trial-related duties and functions. I will maintain a list of sub-investigators and appropriately qualified persons to whom I have delegated significant trial-related duties.

I will provide copies of the study protocol and IB to all participating physicians under my supervision. I will discuss these materials with them to ensure they fully understand the medical technology involved and the conduct of the study.

I will not enroll any subject until I obtain EC/IRB approval and the requirements of Chinese laws and regulations are fully met (if applicable).

I will provide my curriculum vitae and those of my staff before the study commences. I agree that, if necessary, the information can be submitted to relevant government authorities and archived as part of the trial master files.

Signing the study protocol means that I agree to:

▫ conduct the clinical study in compliance with ICH-GCP, with the applicable regulatory requirements, and with the protocol given approval/favorable opinion by the IRB/IEC;

▫ comply with procedures for data recording/reporting;

▫ permit monitoring and auditing by the sponsor, inspection by the appropriate regulatory authorities, and EC/IRB review and retain the trial-related essential documents in accordance with relevant laws and regulations.

PROTOCOL SYNOPSIS

Study title:
Phase I Study of Pegylated Liposomal Doxorubicin (Duomeisu®) Combined with Cyclophosphamide and Vincristine in Pediatric Patients with Relapsed/Refractory Solid Tumor

Study No.:
CSPC-DMS-PO-01

Stage phase:
Phase I

Study site:
Sun Yat-sen University Cancer Center

Principal investigators:
Prof. Yizhuo Zhang and Prof. Xiaofei Sun

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Background:
Doxorubicin, an anthracycline antibiotic, has become a standard component of treatment for many pediatric tumors. However, its long-term cardiotoxicity is a significant concern. Pegylated liposomal doxorubicin (PLD) is a new liposomal formulation of doxorubicin hydrochloride (C27H29NO11•HCl). Pegylated liposomes contain surface-grafted segments of the hydrophilic polymer methoxy polyethylene glycol (MPEG). These linear MPEG groups extend from the liposome surface to create a protective coating that reduces the interaction between the lipid bilayer membrane and the plasma components. This allows doxorubicin to evade the human immune system and circulate for prolonged time in the blood stream. The drug is encapsulated in liposomes, which reduces the peak plasma concentration of free drug and allows targeted delivery to tumor cells through neovascularization, significantly reducing non-specific distribution to normal tissues. While improving the antitumor effect, PLD also reduces major toxic and side effects associated with conventional doxorubicin, such as cardiotoxicity, alopecia, nausea, vomiting, and bone marrow suppression.

Both the pharmacokinetics (PK) data from the Phase I dose escalation study in children with solid tumors and findings from the Phase II clinical study in children with progressive soft tissue sarcoma of Caelyx (PLD) have shown that the Caelyx has a good safety profile. PLD (Duomeisu®) was developed and produced by CSPC Ouyi Pharmaceutical Co., Ltd. It was officially launched in February 2012 and its registration type is Class 6 generic drug according to the current drug registration system of China. Prior to marketing, a randomized, double-blind, crossover trial of Duomeisu® (50 mg/m^2) was conducted in 24 subjects to evaluate its PK, which showed that Duomeisu® is bioequivalent to Caelyx.

The long-term cardiotoxicity of drugs in pediatric cancer survivors cannot be ignored. In order to improve their quality of life and minimize cardiotoxicity, the selection of drugs that pose less cardiotoxicity but preserve overall survival (OS) is crucial. Compared to conventional doxorubicin, PLD stands out primarily for its reduced cardiotoxicity.

Duomeisu® is currently approved for use in patients with AIDS-associated Kaposi's sarcoma (AIDS-KS) with low CD4 counts (< 200 CD4 lymphocytes/mm^3) and extensive skin, mucosal, or visceral disease. At present, there are no data on its use in pediatric tumors. In view of the forementioned facts, we plan to conduct a Phase I study of PLD (Duomeisu®) in combination with cyclophosphamide and vincristine in children with relapsed/refractory solid tumors to determine the maximum tolerated dose (MTD) and safety of Duomeisu® in pediatric patients with solid tumors, thereby laying the foundation for subsequent Phase II/III clinical studies.

Study objectives:

Objectives of Phase Ia Study

Primary objectives: To evaluate the safety, and determine the DLT and MTD of PLD in combination with cyclophosphamide and vincristine in children with relapsed/refractory solid tumors.

Secondary objectives: To describe the antitumor activity of PLD in combination with cyclophosphamide and vincristine in children with relapsed/refractory solid tumors. The observation indexes include ORR and DCR.

Exploratory objective: To explore the PFS of the combination of PLD, cyclophosphamide, and vincristine in children with relapsed/refractory solid tumors. PFS was defined as the time from the enrollment to the occurrence of disease progression or death from any cause or time of last follow-up if no event had occurred.

Objectives of Phase Ib Study

Primary objectives: To evaluate the safety of PLD in combination with cyclophosphamide and vincristine in children with relapsed/refractory solid tumors.

Secondary objectives: To describe the antitumor activity of PLD in combination with cyclophosphamide and vincristine in children with relapsed/refractory solid tumors. The observation indexes include ORR and DCR.

Exploratory objective: To explore the PFS of the combination of PLD, cyclophosphamide, and vincristine in children with relapsed/refractory solid tumors. PFS was defined as the time from the enrollment to the occurrence of disease progression or death from any cause or time of last follow-up if no event had occurred.

Study design:

Phase Ia: dose escalation study

A Phase Ia dose escalation study of PLD in combination with cyclophosphamide and vincristine in children with relapsed/refractory solid tumors.

It is a single-center, single-arm, open-label Phase I dose escalation study with a standard 3 + 3 design.

Phase Ib: expansion cohorts

- To enroll an additional 9 or more patients in the expansion cohorts after the formal dose escalation phase of the study to confirm the established safe exposure level of the drug;

- To enroll children with relapsed/refractory solid tumors (same patient population as the Phase Ia dose escalation cohorts) in the Phase Ib dose expansion cohorts.

Study population:

Pediatric patients with pathologically confirmed relapsed/refractory solid tumors who have failed the first-line treatment.

Inclusion criteria:

1) Age: 1–18 years old;
2) ECOG PS score: 0–1;
3) Pediatric patients with pathologically confirmed solid tumors;
4) Patients with relapsed/refractory (defined as failing to achieve a CR or PR after the last treatment) conditions after the first-line treatment;
5) Patients must have at least one RECIST-defined measurable lesion;
6) Life expectancy: ≥ 6 months;
7) Cardiac function:
   a) Left ventricular ejection fraction (LVEF) ≥ 50% as assessed by echocardiography;
   b) No evidence of myocardial ischemia on the electrocardiography (EKG);
   c) No medical history of arrhythmias requiring pharmacological interventions prior to enrollment;
8) Patients must have completely recovered from prior antitumor chemotherapy-associated acute toxicities;
   a) Myelosuppressive chemotherapy: at least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea is used);
   b) Other investigational drug or antitumor therapy: must not be received within 28 days before enrollment; if previously used, clear evidence demonstrating a complete recovery from any clinically significant toxicity associated with such therapy is required;
   c) Hematopoietic growth factors: at least 14 days after the last dose of a long-acting growth factor or 3 days after the last dose of a short-acting growth factor;
   d) Immunotherapy: at least 42 days after the completion of any type of immunotherapy (excluding steroids), such as immune checkpoint inhibitors and tumor vaccines;
   e) X-ray therapy (XRT): at least 14 days after local palliative XRT (small port); at least 42 days after the end of other substantial bone marrow (BM) radiation, including prior treatment with radioactive ^{131}iodine-metaiodobenzylguanidine (^{131}I-MIBG);
   f) Stem cell infusion without total body irradiation (TBI): at least 56 days after stem cell transplantation or infusion with no evidence of active Graft-versus-Host Disease (GVHD);
9) For patients known to have no BM involvement:
   a) Absolute neutrophil count (ANC) ≥ 1.0×10^9/L;
   b) Platelet count (PLT) ≥ 100.0×10^9/L;
   c) Hemoglobin (HB) ≥ 90 g/L;
10) Patients must have an adequate hepatic and renal function, defined by:
   a) Total bilirubin (bound + unbound) ≤ 2.5 × upper limit of normal (ULN) (corresponding to age); patients with confirmed Gilbert's syndrome may be enrolled at the investigator's discretion;
   b) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 2.5 × ULN;
   c) Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2 or serum creatinine (Cr) ≤ 1.5 × ULN;
11) Patients are able to comply with outpatient treatment, laboratory monitoring, and required clinical visits procedures during the study;
12) Parents/guardians of pediatric or adolescent subjects are able to understand, consent, and sign an informed consent form (ICF) and applicable child assent form prior to initiation of any protocol-related procedures; subjects are able to give assent (if applicable) upon parental/guardian consent.

Exclusion criteria:

1) History of prior or concurrent clinically significant active cardiovascular diseases, including congenital heart disease or pericardial disease; history of heart failure, myocardial infarction, coronary artery disease, heart valve disease, cardiomyopathy, or arrhythmia (including persistent atrial fibrillation, complete left bundle branch block, frequent premature ventricular complex); or QTc prolongation > 480 ms after correction for the current heart rate;
2) History of severe chronic skin diseases;

3) History of allergic asthma or severe allergic diseases;
4) Poorly controlled hypertension or diabetes mellitus;
5) Medical history of other tumors, except for cured cervical cancer or basal cell carcinoma of the skin;
6) Positive hepatitis B surface antigen;
7) HIV or syphilis infection;
8) History of organ transplant;
9) Uncontrolled active systemic bacterial, viral, or fungal infection;
10) Contraindications to high-dose hormone therapy, such as uncontrolled hyperglycemia, gastric ulcer, or psychiatric illness;
11) Patients who have received a total cumulative dose of doxorubicin ≥ 450 mg/m^2 or of epirubicin ≥ 550 mg/m^2, or those who experienced cardiac lesions from prior treatment with anthracyclines;
12) Medical history of severe neurological or psychiatric illness, including epilepsy or autism.

Criteria for discontinuation of study treatment:

1) Withdrawal of informed consent;
2) Treatment discontinuation at the discretion of the investigator;
3) Disease progression or death of patients;
4) Serious non-compliance with the study protocol;
5) Inability to continue study treatment due to other serious toxicities;
6) Study endpoint achieved: Determination of the MTD.

Study protocol:

1) Chemotherapy regimen of PLD in combination with cyclophosphamide and vincristine, once every 3 weeks for 2 cycles. After completing two cycles, the investigators and patients' guardians decided whether to continue the protocol.
2) Administration of PLD: dilute in 250 mL of 5% GS, and slowly infuse over 90 min (a maximum rate of 1 mg/min in the first 30 mins);
3) Dosage and administration of cyclophosphamide: dilute in 100 mL of 0.9% NS, and infuse at 1500 mg/m^2/d on D1, followed by a rescue therapy with mesna at a 1:1 ratio with cyclophosphamide in three equal doses;
4) Dosage and administration of vincristine: dilute in 20 mL of 0.9% NS, and administer via intravenous (IV) push at 1.5 mg/m^2 on D1 (≯ 2 mg).

Planned sample size:

Phase Ia: In the dose escalation study, up to 36 patients are planned to be enrolled to determine the MTD of PLD. The sample size will vary depending on the level at which the MDT is determined;
Phase Ib: Approximately an additional 9 or more patients may be enrolled in the dose expansion cohorts.

Study endpoints:

Phase Ia

Primary endpoints:

- MTD of PLD.
- Safety of PLD in combination with cyclophosphamide and vincristine, including hematological and non-hematological toxicities, and clinical and subclinical cardiotoxicity (NCI CTCAE v5.0).

Secondary endpoints:

- Objective response rate (ORR): complete response (CR) + partial response (PR) (see Appendix 1 for evaluation criteria). Disease control rate (DCR): CR + PR + stable disease (SD) (see Appendix 1 for evaluation criteria).

Phase Ib

Primary endpoint: Safety of PLD in combination with cyclophosphamide and vincristine, including hematological and non-hematological toxicities, and clinical and subclinical cardiotoxicity (NCI CTCAE v5.0).

Secondary endpoints:

- ORR: CR + PR (see Appendix 1 for evaluation criteria). DCR: CR + PR + SD (see Appendix 1 for evaluation criteria).

This study is a Phase I dose escalation study using a standard 3 + 3 design, with efficacy and adverse events (AEs) analyzed and presented in the form of percentages.

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LIST OF ABBREVIATIONS

Abbreviation	Full name
CHF	Congestive heart failure
LVEF	Left ventricular ejection fraction
RNA	Radionuclide angiography
PLD	Pegylated liposomal doxorubicin
MTD	Maximum tolerated dose
DLT	Dose-limiting toxicity
ORR	Overall response rate
PFS	Progression free survival
OS	Overall survival
ANC	Absolute neutrophil count
PLT	Platelets
HB	Hemoglobin
WBC	White blood cell
MPEG	Methoxy polyethylene glycol
PK	Pharmacokinetics
AIDS-KS	AIDS-associated Kaposi's sarcoma
DCR	Disease control rate
EKG	Electrocardiography
XRT	X-ray therapy
BM	Bone marrow
^{131}I-MIBG	^{131}iodine-metaiodobenzylguanidine
TBI	Total body irradiation
GVHD	Graft-versus-Host Disease
ULN	Upper limit of normal
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ICF	Informed consent form

IV	Intravenous
CR	Complete response
PR	Partial response
SD	Stable disease
RP2D	Recommended Phase II dose
RMS	Rhabdomyosarcoma
EWS	Ewing sarcoma
PEG-rhG-CSF	Pegylated recombinant human granulocyte colony-stimulating factor
CRF	Case report form
rhG-CSF	Recombinant human granulocyte colony-stimulating factor
TPO	Thrombopoietin
TCM	Traditional Chinese medicine
NEUT	Neutrophil count
LYM	Lymphocyte count
RBC	Red blood cell
NT-proBNP	N-terminal pro-brain natriuretic peptide
M	Myoglobin
MRI	Magnetic resonance imaging
CK-MB	Creatine kinase-MB
LV	Left ventricular
FS	Fractional shortening
EF	Ejection fraction
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
PD	Progressive disease
LD	Longest diameter
SAEs	Serious adverse events
SUSARs	Suspected unexpected serious adverse reactions
FAS	Full analysis set

ADL	Activity of daily living
RECIST	Response Evaluation Criteria in Solid Tumors
IB	Investigator's Brochure
CT	Computed tomography

1. BACKGROUND

Doxorubicin, an anthracycline antibiotic, has become a standard component of treatment for many pediatric tumors, with dose-limiting cardiotoxicity as its major adverse reaction. The mechanism of doxorubicin-induced cardiotoxicity primarily involves lipid peroxidation driven by oxygen free radicals, leading to myocyte vacuolization, injury, and eventual replacement with fibrotic tissue, a process that is usually irreversible[1]. An early study showed that the cumulative probability of developing congestive heart failure (CHF) in patients receiving a cumulative doxorubicin dose of 400 mg/m², 550 mg/m², and 700 mg/m² was 3%, 7%, and 18%, respectively. Therefore, a maximum cumulative dose of doxorubicin of 550 mg/m² is recommended in the clinical setting[2]. However, studies in recent years indicated that this probability has been significantly underestimated. An analysis of 630 doxorubicin-treated patients from three randomized trials by Swain *et al.* showed that the cumulative probability of developing CHF was 5%, 16%, 26%, and up to 48% respectively in patients receiving a cumulative doxorubicin dose of 400 mg/m², 500 mg/m², 550 mg/m², and > 650 mg/m²[3]. In the clinical use of adriamycin, aside from monitoring the cumulative dose, regular assessment of post-treatment changes in the left ventricular ejection fraction (LVEF) is essential to monitor clinical cardiotoxicity, which is typically determined through radionuclide angiography (RNA) or electrocardiography (EKG). An LVEF of less than 50% or a decrease of more than 10% to 15% from baseline is defined as subclinical cardiotoxicity, a condition that often warrants discontinuation of doxorubicin in subsequent chemotherapies to prevent CHF.

Efforts have been made in clinical practice to effectively reduce doxorubicin-induced cardiotoxicity, thereby overcoming the DLT of doxorubicin, such as the use of dexrazoxane as an antidote, but the results remain unsatisfactory. PLD is a new liposomal formulation of doxorubicin hydrochloride (C27H29NO11•HCl). Pegylated liposomes contain surface-grafted segments of the hydrophilic polymer MPEG. These linear MPEG groups extend from the liposome surface to create a protective coating that reduces the interaction between the lipid bilayer membrane and the plasma components. This allows doxorubicin to evade the human immune system and circulate for prolonged time in the blood stream. The drug is encapsulated in liposomes, which reduces the peak plasma concentration of free drug and allows targeted delivery to tumor cells through neovascularization, significantly reducing non-specific distribution to normal tissues. While improving the antitumor effect, PLD also reduces major toxic and side effects associated with conventional doxorubicin, such as cardiotoxicity, alopecia, nausea, vomiting, and bone marrow suppression[4–6].

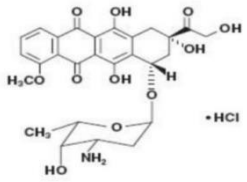
PLD is characterized by PEG-modified liposomes, which prevent phagocytosis by mononuclear macrophages, resulting in a significantly prolonged half-life (55 h), more than ten times that of conventional doxorubicin.

In a Phase III randomized controlled study comparing PLD (50 mg/m^2, every 4 weeks) with conventional doxorubicin (60 mg/m^2, every 3 weeks) as monotherapy in advanced breast cancer, the risk of cardiotoxicity in patients receiving conventional doxorubicin was 3.16 times higher than that in patients receiving PLD ($P < 0.001$), whereas there was no difference in the efficacy between the two groups[7]. Schmitt *et al.* retrospectively analyzed the data of 21 NHL patients with LVEF dysfunction or high-risk factors for cardiotoxicity, all of whom were treated with PLD instead of conventional doxorubicin as a component of the CHOP regimen[8]. The results showed that the ORR was 85%, no significant cardiac dysfunction was observed in 20 patients after treatment, and hand-foot syndrome was the leading cause of treatment discontinuation. Another prospective Phase II clinical study involving 94 eligible patients was

conducted to investigate the efficacy of PLD (Caelyx) versus conventional doxorubicin in patients with progressive or metastatic soft tissue sarcoma. The results showed that PLD (50 mg/m^2, every 4 weeks) was equivalent in efficacy to conventional doxorubicin (75 mg/m^2, every 3 weeks), but resulted in a significantly lower incidence of Grade ≥ 3 neutropenia than conventional doxorubicin (6% *vs.* 77%)[9].

In a Phase I clinical trial of Caelyx (PLD) in pediatric solid tumors[10], pediatric patients with relapsed or refractory solid tumors were enrolled to receive a cumulative anthracycline dose of < 300 mg/m^2 to investigate the MTD and PK. The results showed that the DLT among patients at 70 mg/m^2 was mucositis. Therefore, the MTD was determined to be 60 mg/m^2, and the recommended Phase II dose (RP2D) was 60 mg/m^2 once every 4 weeks. In a Phase II clinical study investigating the safety, efficacy, and toxicity of Caelyx (PLD) as monotherapy in 8 patients aged ≤ 16 years with metastatic or refractory rhabdomyosarcoma (RMS), Ewing sarcoma (EWS) or osteosarcoma, Caelyx demonstrated good safety and showed efficacy in 3 patients[11].

PLD (Duomeisu®) was developed and produced by CSPC Ouyi Pharmaceutical Co., Ltd. It was officially launched in February 2012 and its registration type is Class 6 generic drug according to the current drug registration system of China. Duomeisu® and Caelyx are of the same molecular subtype. Prior to marketing, a randomized, double-blind, crossover trial of Duomeisu® (50 mg/m^2) was conducted in 24 subjects to evaluate its PK, which showed that Duomeisu® is bioequivalent to Caelyx. The chemical structural formula of PLD (Duomeisu®) is shown below: Molecular formula: $C_{27}H_{29}NO_{11}\cdot HCl$, molecular weight: 579.99.



In summary, PLD outperforms conventional doxorubicin primarily for its reduced cardiotoxicity. Duomeisu® is currently approved for use in patients with AIDS-associated Kaposi's sarcoma (AIDS-KS) with low CD4 counts (< 200 CD4 lymphocytes/mm^3) and extensive skin, mucosal, or visceral disease. At present, there are no data on its use in pediatric tumors. In view of the above-mentioned facts, we plan to conduct a Phase I dose escalation study of PLD in children with solid tumors to determine the MTD in pediatric patients with solid tumors, thereby laying the foundation for subsequent combination therapies and Phase II/III clinical studies.

2. STUDY OBJECTIVES

2.1 Objectives of Phase Ia Study

Primary objectives: To evaluate the safety, and determine the DLT and MTD of PLD in combination with cyclophosphamide and vincristine in children with relapsed/refractory solid tumors.

Secondary objectives: To describe the antitumor activity of PLD in combination with cyclophosphamide and vincristine in children with relapsed/refractory solid tumors. The observation indexes include ORR and DCR.

Exploratory objective: To explore the PFS of the combination of PLD, cyclophosphamide, and vincristine in children with relapsed/refractory solid tumors. PFS was defined as the time from the enrollment to the occurrence of disease progression or death from any cause or time of last follow-up if no event had occurred.

2.2 Objectives of Phase Ib Study

Primary objectives: To evaluate the safety of PLD in combination with cyclophosphamide and vincristine in children with relapsed/refractory solid tumors.

Secondary objectives: To describe the antitumor activity of PLD in combination with cyclophosphamide and vincristine in children with relapsed/refractory solid tumors. The observation indexes include ORR and DCR.

Exploratory objective: To explore the PFS of the combination of PLD, cyclophosphamide, and vincristine in children with relapsed/refractory solid tumors. PFS was defined as the time from the enrollment to the occurrence of disease progression or death from any cause or time of last follow-up if no event had occurred.

3. STUDY ENDPOINTS

3.1 Endpoints of Phase Ia Study

Primary endpoints:

- MTD of PLD.
- Safety of PLD in combination with cyclophosphamide and vincristine, including hematological and non-hematological toxicities, and clinical and subclinical cardiotoxicity (NCI CTCAE v5.0).

Secondary endpoints:

- ORR: CR + PR (see Appendix 1 for evaluation criteria).
- DCR: CR + PR + SD (see Appendix 1 for evaluation criteria).

3.2 Endpoints of Phase Ib Study

Primary endpoints: Safety of PLD in combination with cyclophosphamide and vincristine, including hematological and non-hematological toxicities, and clinical and subclinical cardiotoxicity (NCI CTCAE v5.0).

Secondary endpoints: ORR: CR + PR (see Appendix 1 for evaluation criteria). DCR: CR + PR + SD (see Appendix 1 for evaluation criteria).

4. STUDY DESIGN

1) **Phase Ia dose escalation study**

A Phase Ia dose escalation study of PLD in combination with cyclophosphamide and vincristine in children with relapsed/refractory solid tumors.

It is a single-center, single-arm, open-label Phase I dose escalation study with a standard 3 + 3 design.

2) **Phase Ib expansion cohorts**

An additional 9 or more patients can be enrolled in the expansion cohorts after the formal dose escalation phase of the study to confirm the established safe exposure level of the drug. Children with relapsed/refractory solid tumors (same patient population as the Phase Ia dose escalation cohorts) will be enrolled in the Phase Ib expansion cohorts.

5. SUBJECTS

For pediatric patients with pathologically confirmed solid tumors, their legal guardians must sign an ICF.

5.1 Inclusion Criteria

1) Age: 0–18 years old;

2) ECOG PS score: 0–1;

3) Pediatric patients with pathologically confirmed solid tumors;

4) Patients with relapsed/refractory (defined as failing to achieve a CR or PR after the last treatment) conditions after the first-line treatment;

5) Patients must have at least one RECIST- or WHO-defined measurable lesion;

6) Life expectancy ≥ 6 months;

7) Cardiac function:

a) LVEF ≥ 50% as assessed by echocardiography;

b) No evidence of myocardial ischemia on the EKG;

c) No medical history of arrhythmias requiring pharmacological interventions prior to enrollment;

8) Patients must have completely recovered from prior antitumor chemotherapy-associated acute toxicities;

a) Myelosuppressive chemotherapy: at least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea is used);

b) Other investigational drug or antitumor therapy: must not be received within 28 days before enrollment; if previously used, clear evidence demonstrating a complete recovery from any clinically significant toxicity associated with such therapy is required;

c) Hematopoietic growth factors: at least 14 days after the last dose of a long-acting growth factor (e.g., Pegylated Recombinant Human Granulocyte Colony-Stimulating Factor Injection) or 3 days after the last dose of a short-acting growth factor;

d) Immunotherapy: at least 42 days after the completion of any type of immunotherapy (excluding steroids), such as immune checkpoint inhibitors and tumor vaccines;

e) XRT: at least 14 days after local palliative XRT (small port); at least 42 days after the end of other substantial BM radiation, including prior treatment with radioactive ^{131}I-MIBG;

f) Stem cell infusion without TBI: at least 56 days after stem cell transplantation or infusion with no evidence of active GVHD;

9) For patients known to have no BM involvement:

a) ANC $\geqslant 1.0 \times 10^9$/L;

b) PLT $\geqslant 100.0 \times 10^9$/L;

c) HB $\geq$ 90 g/L;

10) Patients must have an adequate hepatic and renal function, defined by:

a) Total bilirubin (bound + unbound) $\leq$ 2.5 × upper limit of normal (ULN) (corresponding to age); patients with confirmed Gilbert's syndrome may be enrolled at the investigator's discretion;

b) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\leq$ 2.5 × ULN;

c) Estimated glomerular filtration rate $\geq$ 30 mL/min/1.73 m^2 or serum creatinine (Cr) $\leq$ 1.5 × ULN;

11) Patients are able to comply with outpatient treatment, laboratory monitoring, and required clinical visits procedures during the study;

12) Parents/guardians of pediatric or adolescent subjects are able to understand, consent, and sign an ICF and applicable child assent form prior to initiation of any protocol-related procedures; subjects are able to give assent (when applicable) upon parental/guardian consent.

5.2 Exclusion Criteria

1) History of prior or concurrent clinically significant active cardiovascular diseases, including congenital heart disease or pericardial disease; history of heart failure, myocardial infarction, coronary artery disease, heart valve disease, cardiomyopathy, or arrhythmia (including persistent atrial fibrillation, complete left bundle branch block, frequent premature ventricular complex); or QTc prolongation > 480 ms after correction

for the current heart rate;

2) History of severe chronic skin diseases;

3) History of allergic asthma or severe allergic diseases;

4) Poorly controlled hypertension and diabetes mellitus;

5) Medical history of other tumors, except for cured cervical cancer or basal cell carcinoma of the skin;

6) Positive hepatitis B surface antigen;

7) HIV or syphilis infection;

8) History of organ transplant;

9) Uncontrolled active systemic bacterial, viral, or fungal infection;

10) Contraindications to high-dose hormone therapy, such as uncontrolled hyperglycemia, gastric ulcer, or psychiatric illness;

11) Patients who have received a total cumulative dose of doxorubicin ≥ 450 mg/m^2 or of epirubicin ≥ 550 mg/m^2, or those who experienced cardiac lesions from prior treatment with anthracyclines;

12) Medical history of severe neurological or psychiatric illness, including epilepsy or autism.

5.3 Criteria for Discontinuation of Study Treatment

1) Withdrawal of informed consent;

2) Treatment discontinuation at the discretion of the investigator;

3) Disease progression or death of patients;

4) Serious non-compliance with the study protocol;

5) Inability to continue study treatment due to other serious toxicities;

6) Study endpoint achieved: determination of the MTD.

6. STUDY PROTOCOL

6.1 Chemotherapy Regimen

1) Chemotherapy regimen of PLD in combination with cyclophosphamide and vincristine, once every 3 weeks for 2 cycles. After completing two cycles, the investigators and patients' guardians decided whether to continue the protocol.

2) Administration of PLD: dilute in 250 mL of 5% GS, and slowly infuse for > 90 min (a maximum rate of 1 mg/min in the first 30 min);

3) Dosage and administration of cyclophosphamide: dilute in 100 mL of 0.9% NS, and infuse at 1500 g/m^2/d on D1, followed by a rescue therapy with mesna at a 1:1 ratio with cyclophosphamide in three equal doses.

4) Dosage and administration of vincristine: dilute in 20 mL of 0.9% NS, and administer via IV push at 1.5 mg/m^2 on D1 ($\prec$ 2 mg).

6.2 Determination of the Maximum Tolerated Dose

1) Patients are enrolled per the design of the Phase I study. Three dose levels are set, i.e., 30 mg/m^2, 40 mg/m^2, and 50 mg/m^2. Dose escalation of PLD is performed successively from the lowest dose level;

2) Three patients are initially enrolled into a given dose cohort and the DLT is observed in the Cycle 1:

   - If there is no DLT observed in any of these subjects, the next higher dose cohort is opened;

   - If one subject develops a DLT at a specific dose, an additional three subjects are enrolled into that same dose cohort. If there is no DLT observed in the additional three subjects, further dose escalation is pursued. If there is one or more DLT observed in the additional three subjects, further dose escalation is not pursued.

   - If two or more of the three subjects develop DLTs, go back to the lower dose level;

3) MTD is defined as the dose below the level at which the DLT is determined. If the DLT is observed at the first dose level (30 mg/m^2), go back to level -1 (25 mg/m^2);

4) An additional six patients will be treated at the MTD. If no or one subject develops a DLT, the dose is defined as the final MTD;

5) If the MTD is still not determined after dose escalation to the 3rd level, the dose at this level (50 mg/m^2) is determined to be the final MTD.

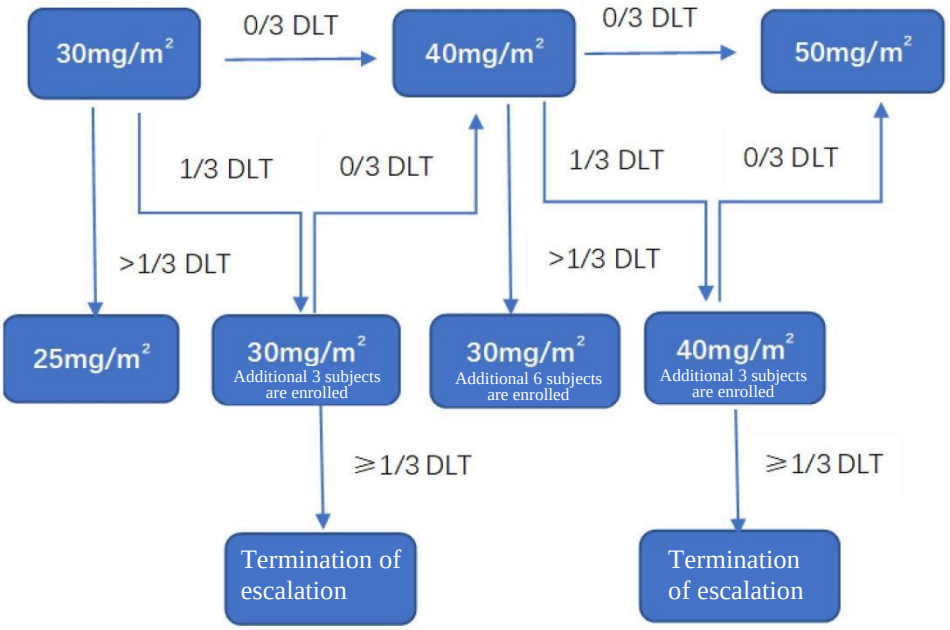


Figure 1. Schematic diagram of the 3 + 3 dose escalation rules

6.3 Definition of Dose-limiting Toxicity

(Evaluation criteria: NCI CTCAE v5.0)

Following toxicities that are observed after the treatment with pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) at 48 h after the end of chemotherapy are defined as DLTs.

1) Hematology:

- Grade 4 neutropenia for ≥ 7 days;
- Grade 4 thrombocytopenia ≥ 7 days;

2) Grade 3/4 non-hematological toxicities except for nausea, vomiting, and alopecia;

3) Any toxicity-induced chemotherapy delay for more than 2 weeks;

6.4 Definition of Cardiotoxicity

1) Clinical cardiotoxicity: Grade ≥ 2 cardiac dysfunction (NYHA Functional Classification, see Appendix 1);

2) Subclinical cardiotoxicity: an abnormal LVEF

- Criteria: a post-treatment LVEF level of < 50% or a decrease of ≥ 15% from baseline as assessed by findings from pre- and post-treatment echocardiography;

6.5 Concomitant Medications

1) During the observation period, medications other than the investigational drug are all concomitant medications and should be documented in the patient's medical records and case report form (CRF). Concomitant medications in this study will be documented from

the subject's signing of the ICF until 28 days after the end of the study treatment or the initiation of other antitumor therapies (whichever comes first);

2) PEG-rhG-CSF (Jinyouli) will be initiated 48 h after the end of chemotherapy;

3) Prophylactic recombinant human granulocyte colony-stimulating factor (rhG-CSF) or antibiotic is prohibited in Cycle 1;

4) The rhG-CSF can be used discretionarily only when severe neutropenic fever occurs in Cycle 1; in the occurrence of neutropenic fever, standard anti-infective treatment should be administered by following relevant guidelines;

5) Thrombopoietin (TPO) or component transfusion is permitted only when Grade 4 thrombocytopenia occurs in Cycle 1, and the use of IL-11 is not recommended;

6) Any traditional Chinese medicine (TCM)/Chinese patent medicine is prohibited in Cycle 1;

7) There are no restrictions on the use of cytokines in the treatment after Cycle 1;

8) The use of dexrazoxane is prohibited;

9) The use of supportive medications (e.g., antiemetics and analgesics) is permitted.

6.6 Other Considerations

1) The dose (rounding to 2 decimal places) in Cycle 1 should be calculated in strict accordance with the body surface area. Generally, doses in subsequent cycles are determined by referring to the dose in Cycle 1. If the change in weight exceeds 10% while on treatment, the dose should be recalculated;

2) In Cycle 1, hospitalization is required, and hematology tests should be conducted every Monday, Wednesday, and Friday. In the event of Grade 4 neutropenia or Grade 4 thrombocytopenia, or when deemed necessary, the frequency of testing should be increased, such as daily hematology testing. For subsequent cycles, standard medical practices apply to hematology tests;

3) A 5-HT3 receptor antagonist (e.g., palonosetron) should be used as a standard antiemetic treatment;

4) For diabetic patients, attention should be paid to their glycemic control during hormonotherapy;

5) To prevent the occurrence and severity of hand-foot syndrome, patients should be educated to:

- Perform intensive care for their hands and feet by applying alcohol-free moisturizing cream and wearing cotton gloves and socks before bedtime to maximize cream absorption;
- Avoid using skin irritants such as perfume, alcohol, or cleaning products;
- Avoid wearing overly tight, irritating, or uncomfortable underwear and shoes;
- Avoid strenuous, mechanical exercises or maintaining a fixed body position for a long period of time;

- Avoid hip baths, overly hot showers, and vigorous rubbing of the skin with a towel after a shower;
- Avoid intense or direct sunlight or direct sun of afternoon.

7. STUDY ASSESSMENT AND ROUTINE INVESTIGATIONS

7.1 Observation Indicators and Requirements

From an ethical perspective, examinations/tests that have been performed before the subject signs the ICF and meet the requirements specified in the protocol may not be repeated.

7.2 Basic Information and Characteristics of Subjects

1) Demographic data: age, gender, race, height, and weight;
2) Medical history (medical history, tumor treatment history, etc.):
   - ➢ Condition diagnosis: pathological diagnosis, date of initial diagnosis, methods of obtaining pathological tissues, pre-enrollment clinical diagnosis, and clinical stages;
   - ➢ History of surgical treatment: date, reason, and name of the surgery;
   - ➢ History of stem cell transplantation: date, type, and description of the transplantation;
   - ➢ History of chemotherapy: start and end time, regimen description, number of courses, toxicity tolerance, best response, and treatment failure or progressive disease (if any) and their respective dates;
   - ➢ History of radiotherapy: start and end time, site of radiotherapy, total dose, and best response;
   - ➢ History of targeted therapy: start and end time, generic name, number of cycles, toxicity tolerance, best response, and treatment failure or progressive disease (if any) and their respective dates;
   - ➢ History of other antitumor therapies: start and end time, treatment details, and best response;
   - ➢ History of allergy;
   - ➢ Concomitant diseases and concomitant medications: disease diagnosis or symptom description, date of diagnosis, conditions in the screening period, whether symptomatic treatment is administered during the screening period, and treatment details (treatment regimen/generic name, dosage form, dose, frequency of administration, route of administration, start and end time); diseases, except for the tumors, documented within 5 years before signing the ICF;
3) Physical examination: general condition, skin, mucous membranes, head, neck, chest, abdomen, spine/extremities, nervous system, and lymph nodes;

4) ECOG PS scores: refer to Appendix 2;

5) Vital signs: heart rate, blood pressure, body temperature, and respiratory rate;

Efforts must be made to collect the subject's medical history and demographic data as much as possible before the first dose of the investigational drug to confirm compliance with eligibility criteria. Any omitted or corrected medical history and demographic data identified throughout the study must be documented in subsequent raw data.

Physical examination, ECOG PS scoring, and vital sign measurement at screening should be completed within 7 days before randomization; if the acceptable time window is exceeded, they should be repeated.

Subject should be at rest for all vital sign measurements. If the body temperature is measured more than twice a day, the higher one will be documented.

7.3 Laboratory Tests

1) Pre-enrollment: hematology, urinalysis, blood chemistry, coagulation, epidemiology, and cardiac function tests.

2) Each treatment cycle and post-treatment: hematology, blood chemistry, and cardiac function tests.

Table 1. Laboratory tests

Tests	Parameters
Hematology	White blood cell (WBC) count, neutrophil count (NEUT), lymphocyte count (LYM), red blood cell (RBC) count, HB, and PLT
Urinalysis	Urine protein, urine glucose, urine RBCs, and urine WBCs
Blood chemistry	ALT, AST, ALP, LDH, TBIL, DBIL, IBIL, TP, ALB, Cr, Urea, K^+, Na^+, Cl^-, Ca, Mg, and P
Coagulation	INR, APTT, PT, and FIB
Epidemiology	HIV-Ab; HBsAg, HBsAb, HBeAg, HBeAb, HBcAb, and HBV-DNA (when necessary, such as HBsAg- and/or HBcAb-positive); Anti-HCV and HCV RNA (when necessary, such as HCV-positive)
Cardiac function test	Cardiac troponin T, N-terminal pro-brain natriuretic peptide (NT-proBNP), myoglobin (M), and creatine kinase-MB (CK-MB); 12-lead electrocardiogram; echocardiographic including LVEF, left ventricular (LV) systolic (fractional shortening [FS] and biplane Simpson's ejection fraction [EF]).

7.4 Radiological Examination

1) Requirements for examinations: examinations during the study should be performed under the same conditions at baseline. The imaging specifications should refer to the evaluation criteria in Appendix 1 to ensure a rational response evaluation;

2) Pre-enrollment: relevant examinations/tests should be completed according to the evaluation criteria for different tumors, generally including plain + contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis, plain + contrast-enhanced magnetic resonance imaging (MRI) scan, ECT examination, or PET/CT scan; bone marrow aspirate smears;

3) After 2 cycles of treatment: CT or plain + contrast-enhanced MRI of the positive or suspected site for evaluation of tumor response (see Appendix 1 for evaluation criteria).

7.5 12-lead electrocardiogram

1) Perform routinely before enrollment, after 2 cycles of treatment, before each subsequent cycle, at off-study, at every 3-month follow-up in the first year of off-study, at every 6-month follow-up in the second year of off-study, and every 1-year follow-up in the third to fifth years of off-study.

2) Perform at any time during treatment when the patient shows signs of cardiac dysfunction.

7.6 Electrocardiography

1) Perform routinely at baseline, after two cycles of VPC, at off-study, and when reevaluation was necessary.

2) Perform during treatment at any time when the patient shows signs of cardiac dysfunction.

7.7 Cardiac Function Scoring (NYHA Functional Classification, See Appendix 2)

1) Perform routinely before enrollment and each cycle and after the end of chemotherapy;

2) Perform at any time during treatment when the patient shows signs of cardiac dysfunction.

7.8 Risk Factors for Congestive Heart Failure

1) Document potential risk factors for CHF before enrollment;

2) Risk factors: smoking, obesity (body mass index [BMI] > 30 kg/m^2), hypertension, diabetes mellitus, and chronic obstructive pulmonary disease (COPD).

8. DOSE MODIFICATION

8.1 Hematology

1) The dose used in the cycle will be determined based on the strongest hematological toxicity in the previous cycle;

2) If Grade 4 thrombocytopenia occurs, the dose of PLD will decrease by 20%;

3) If Grade 4 neutropenia occurs for < 3 days, the previous dose will be maintained;

4) If Grade 4 neutropenia or neutropenic fever occurs for ≥ 3 days, the dose of PLD will decrease by 20%; prophylaxis with supportive G-CSF or antibiotics may be considered;

8.2 Liver Function

1) If Grade 3/4 hepatic impairment occurs in the previous cycle, the dose of PLD will decrease by 25% in the next cycle;

2) If total bilirubin, ALT, or AST are < 1.5 × UNL before chemotherapy, the previous dose

(100%) will be maintained;

3) If total bilirubin, ALT, or AST is 1.5–3.0 × UNL before chemotherapy, the dose of PLD will decrease by 50%;

4) If total bilirubin, ALT, or AST is > 3.0 × UNL before chemotherapy, the administration will be delayed, and liver protecting treatment will be performed;

5) The attending physician may decide whether to use reduced-dose chemotherapy or to delay chemotherapy and perform liver protecting treatment according to the specific circumstances.

8.3 Cardiac Function

Table 2. Principles of dose modification for cardiac function events

AE	Toxicity grading	Treatment recommendations	Dose modification
Left ventricular systolic dysfunction	1–2	Perform close observation and provide active treatment	Maintain the previous dose
	3–4	Terminate the treatment	--
Bradycardia (heart rate <60 beats/min)	1	Perform close observation and provide active treatment	Maintain the previous dose
	2–3	If the event is assessed to be caused by the subject's concomitant medications, interrupt the treatment until the toxicity is recovered to Grade ≤ 1 or the heart rate reaches ≥ 60 beats/min.	Maintain the previous dose
		If the event is assessed not to be caused by the subject's concomitant medications, interrupt the treatment until the toxicity is recovered to Grade ≤ 1 or the heart rate reaches ≥ 60 beats/min.	Reduce the dose level
	4	If the event is assessed to be caused by the subject's concomitant medications, interrupt the treatment until the toxicity is recovered to Grade ≤ 1 or the heart rate reaches ≥ 60 beats/min, and then perform frequent monitoring	Reduce the dose level; discontinue the treatment if the toxicity recurs
		If the event is assessed not to be caused by the subject's concomitant medications,	Discontinue the treatment
QTc prolongation	1	Perform close observation	Maintain the previous dose
	2	Evaluate electrolytes and concomitant medications, and correct any electrolyte or magnesium disturbance	Maintain the previous dose
	3	Interrupt the treatment until the toxicity is recovered to Grade ≤ 1	Reduce the dose level
	4	Terminate the treatment	--

8.4 Hand-foot Syndrome (See Appendix 2 for Evaluation Criteria)

1) Occurrence of a Grade 1 reaction: give symptomatic supportive treatment and intensive preventive care;

2) Occurrence of a Grade 2 reaction: give symptomatic supportive treatment and intensive preventive care;

- First occurrence: delay the treatment until the reaction is alleviated to Grade 1 and maintain the previous dose;
- Second or subsequent occurrence: delay the treatment until the reaction is alleviated to Grade 1 and decrease the dose of PLD by 25%;

3) Occurrence of a Grade 3 reaction: delay the treatment until the reaction is alleviated to Grade 1 and decrease the dose of PLD by 25%.

9. STUDY ASSESSMENT

9.1 Assessment of Efficacy

9.1.1 Efficacy endpoints

- ORR: the percentage of patients with CR and PR over the total number of patients enrolled.

9.1.2 Tumor evaluation

Objective tumor responses including CR, PR, SD, or progressive disease (PD) will be assessed by the investigator and radiologist according to the RECIST 1.1.

For patients entering the study (including those who prematurely discontinue treatment), their tumor responses should be assessed as objectively as possible, and the tumor progression should be confirmed by radiography.

All patients must have at least one measurable lesion at baseline screening. The tumor burden at the lesion site will be assessed by an independent radiologist through CT or MRI. All lesions should be documented, numbered, and measured at baseline. Skin lesions should be measured and imaged. In the CRF, the selected lesion No. of the patient should not be altered throughout the study. These lesions will be followed using the same examination and coding methods as used during the screening period. The size of target lesions will be recorded in mm. For patients who withdraw from the study treatment for other reasons, imaging-based evaluations will be performed according to the above plan. If the patient is allergic to the contrast agent, an MRI may be used instead of a CT scan.

Target lesions should be calculated for progression by comparison with those with the minimum tumor burden (i.e., the smallest sum diameters previously recorded in the study). In the absence of progression, tumor responses (CR, PR, and SD) will be calculated by comparison with baseline tumor measurements obtained before the initiation of treatment.

If effective tumor evaluation results have been obtained by conventional medical methods within an acceptable time window (within 28 days before the initiation of treatment), tumor evaluation may not be performed during the screening period.

Target lesions will be identified based on the lesion size (longest diameter [LD] of the selected lesion) and whether repeated accurate measurements can be made. Other lesions will be

recorded as "non-target lesions" at baseline, followed throughout the study, and used as a reference for evaluating the tumor response of the patient.

For more information on the evaluation criteria in the RECIST 1.1, please refer to Appendix 3.

A bone scan is required if there are suspected new bone metastases at baseline (bone or joint pain with associated elevations in calcium and alkaline phosphatase). Relevant radiological examination (X-ray or CT scan) should be performed on the known lesions at baseline and at each imaging time point if the patient has known bone metastases or is identified with bone metastases at screening. During the study, bone scans should be performed as medically indicated, such as suspected new bone metastases.

Tumor evaluation should proceed as scheduled when the study treatment is delayed, interrupted, or discontinued.

In addition, the investigator should preclude the possibility of symptomatic deterioration of the suspected PD at each visit. If a suspected PD occurs, a CT or MRI scan should be performed immediately.

Symptomatic deterioration leading to study discontinuation is considered a PD unless the PD is excluded by CT or MRI.

9.2 Assessment of Safety

9.2.1 Safety management plan

Measures will be taken to ensure the safety of subjects participating in the study, including strict inclusion and exclusion criteria, and close monitoring, such as in-hospital monitoring and follow-up, as well as out-of-hospital diary card recording and telephone follow-up.

Safety analysis will be performed based on the safety analysis set.

9.2.2 Adverse events

9.2.2.1 Definition of adverse events

An AE in this study is defined as any untoward medical event in a trial subject administered an investigational drug and which does not necessarily have a causal relationship with this treatment.

9.2.2.2 Assessment of adverse events

The name and severity of AEs will be evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events v5.0 (NCI CTCAE v5.0).

The correlation between AEs and the investigational drug is divided into definitely related, probably related, possibly related, unlikely related, and not related. Investigators should assess the possible association between the AE and the investigational drug by referring to the following 5 criteria as listed in the table. 1) A reasonable relationship exists between the time of drug use and the occurrence of the AEs; 2) the AEs conform to the known adverse reactions of the drug; 3) the AEs cannot be explained by other causes; 4) the AEs will disappear after drug discontinuation; 5) the same AEs will occur again after re-exposure to the drug. AEs that are determined to be definitely related, probably related, or possibly related to the investigational drug are recorded as adverse reactions, and the incidence of adverse reactions

is calculated accordingly.

During the screening period of the study, the patient's condition (e.g., past medical history, diagnosis, or disease) will be assessed, and all relevant changes from baseline will be recorded.

At each visit during the treatment and follow-up periods, the investigator will ask the patient about the occurrence of AEs and serious adverse events (SAEs) and document them in the medical records.

Patients are required to report any AEs that occur during the study, including the onset and end dates. If necessary, accurate information about the AEs can be obtained by asking questions, and AEs are graded according to the CTCAE v5.0.

The investigator should collect written records of all AEs, including the onset date, end date, CTCAE grade, treatment measures taken for the event, measures taken for the study treatment, and outcome.

AEs that occur after the end of the study should be reported only when they are SAEs related to the study treatment.

During the study, patients may be admitted for management purposes or as scheduled prior to the start of the study, and such admissions will not be reported as SAEs as long as they are conducted as scheduled.

Upon completion or termination of the study treatment, patients with Grade 3 or 4 laboratory abnormalities should undergo additional testing until these abnormalities return to Grade 1 or 2, unless the underlying disease precludes improvement in these abnormalities.

9.2.2.3 Definition of adverse events

An AE is any untoward medical event or worsening of a pre-existing medical condition that occurs during or after drug administration, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended symptoms (such as nausea or chest pain), signs (such as tachycardia or liver enlargement), or abnormal findings from laboratory tests or EKG. In clinical studies, an AE is any untoward medical event that occurs at any time, including during the run-in or wash-out period, even if no study treatment has been administered. The term AE also includes serious and non-serious AEs.

9.2.2.4 Time of adverse event collection

AEs will be collected from the signing of the ICF until the end of the study.

9.2.2.5 Follow-up of adverse events

AEs should be followed until the disease is stable, normalized, or returns to the pre-treatment level. All AEs and SAEs of each patient should be actively followed throughout the study. Every effort should be made to achieve resolution of all events, even if they persist after discontinuation or termination of the study. At the patient's last visit, any unresolved AE should be followed by the investigator whenever deemed medically necessary, but further follow-up information need not be recorded in the CRF.

9.2.2.6 Adverse event reporting

AE records should include the common terminology, start time, end time, severity, correlation

with the investigational drug, follow-up, outcome, and treatment measures taken.

9.2.2.7 Serious adverse events

During the study, any medical event that meets any of the following five criteria can be defined as an SAE.

9.2.2.8 Definition of serious adverse events

During the study, an SAE is defined as any medical event that:

1) Results in death;

2) Requires inpatient hospitalization or prolongation of existing hospitalization;

3) Is life-threatening;

4) Results in persistent or significant disability/incapacity;

5) Is a congenital anomaly/birth defect.

The following conditions will not be reported as SAEs:

1) Hospitalization for the use of the investigational drug;

2) Hospitalization due to relevant protocol-specified procedures (e.g., pathological tissue sampling). However, inpatient hospitalization or prolonged hospitalization caused by other complications resulting from such procedures should be regarded as an SAE;

3) Scheduled hospitalization due to illness.

9.2.2.9 Suspected unexpected serious adverse reactions definitely related to the investigational drug

Suspected unexpected serious adverse reactions (SUSARs) that are observed during the study period and are definitely related to the investigational drug should be expeditiously reported by the sponsor during the study with reference to the *Standards and Procedures for Expedited Reporting of Safety Data During Drug Clinical Trials* issued by the Center for Drug Evaluation on Apr. 27, 2018. The investigator is obliged to cooperate with the sponsor in the collection and discussion of relevant data.

9.2.2.10 Variables

For each AE, the following variables will be collected:

- AE (terminology)
- Start and end dates and time of the AE
- The highest CTCAE grade reported
- Serious or non-serious AE
- Causal relationship with the medical technology under study as determined by the investigator (yes or no)

- Measures taken for the medical technology under study
- Treatments applied to the AE
- Withdrawal of patients from the study due to the AE (yes or no)
- Outcome of the AE

In addition, the following variables are also collected for SAEs:

- Date when the AE meets the criteria for SAEs
- Date when the investigator is aware of the SAE
- Severity criteria met
- Date of hospitalization
- Date of discharge
- Possible cause of death
- Date of death
- Necropsy or not
- Evaluation of the causal relationship with study procedures
- Description of AE

The grade table in the revised NCI CTCAE v5.0 will be used for all events assigned a CTCAE grade. For events that are not assigned a CTCAE grade, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used.

9.2.2.11 Causality collection

The investigator will evaluate the causal relationship between the therapeutic drug/technology and each AE and answer "yes" or "no" to the following question: Do you think there is a reasonable probability that this event is caused by the investigational product/technology?

The causal relationship between other drugs and study procedures and SAEs will also be evaluated. Note that the causal relationship implies "yes" for SAEs that are related to any study procedure.

Causality assessment between AEs and study treatments is described in Appendix 3.

9.2.2.12 Relationship with procedures in the protocol

The investigator should also record in the SAE report form an assessment of the relationship between SAEs and procedures in the protocol. The events include non-treatment-emergent SAEs (i.e., SAEs that occur before use of the investigational product) and treatment-emergent SAEs. The occurrence of a protocol-related SAE may be the result of a procedure or intervention required during the study (such as blood drawing). The investigator should assess the relationship between SAEs and the protocol using the following guidelines:

- Protocol-related: the occurrence of the event is associated with a procedure or intervention

described in the protocol, and cannot be explained by other causes in the patient's medical record.

- Non-protocol-related: the occurrence of the event is associated with an etiology rather than the procedure or intervention described in the protocol. The other etiology must be recorded in the trial patient's medical record.

9.2.2.13 Serious adverse event reporting

All SAEs should be reported, regardless of whether or not they are considered related to the investigational product or study procedures. All SAEs will be recorded in the CRF.

If any SAE occurs during the study, the investigator should report it to the institution and the hospital's Division of Medical Affairs; fatal and life-threatening events must be reported **within 1 calendar day,** and all other SAEs **within 5 calendar days** upon initial receipt of the information, respectively.

The principal investigator will be responsible for ensuring that procedures and expertise are available to manage medical emergencies during the study. Medical emergencies generally constitute and will be reported as SAEs.

10. STUDY DATA MANAGEMENT

According to the clinical study protocol, the investigator should ensure the accuracy, completeness, and timeliness of data and answers to questions.

The investigator will record the observed data and test results in the patient's medical record and evaluate them according to the protocol.

11. STATISTICAL ANALYSIS

11.1 Statistical Hypotheses

This is a single-arm exploratory study, and no statistical hypothesis test will be performed.

11.2 Sample Size Estimation

This is a Phase I dose escalation study using a standard 3 + 3 design for enrollment. The exact sample size depends on the level at which the MDT is determined.

11.3 Statistical Analysis Method

Efficacy and AEs will be analyzed in the form of percentages.

11.4 Distribution of Subjects

Enrollment, completion, reasons for premature withdrawal, and the conditions of each analysis set population will be summarized. Subjects with premature withdrawal and protocol

deviations will be listed.

11.5 Baseline Information

Descriptive statistics will be provided for baseline demographic data, past medical history (medical history, tumor treatment history, etc.), physical examination findings, ECOG PS scores, and vital signs. Measurement data will be expressed as mean, standard deviation, median, minimum, and maximum; count data will be presented as frequency and percentage.

11.6 Efficacy Analyses

ORR: Proportion of subjects with confirmed disease evaluated as CR + PR. Based on the full analysis set (FAS) population, the frequency and percentage will be listed, and their 95% confidence intervals will be estimated using the Clopper-Pearson method.

12. STUDY MANAGEMENT

12.1 Ethics Review

The investigator should have submitted the trial-related documents and ICF to the Institutional Review Board and Ethics Committee of the Sun Yat-Sen University Cancer Center before the commencement of the study at the site. The Ethics Committee will review the study protocol as required. Any member of the Ethics Committee who is directly involved in the study, such as an investigator or study staff, must recuse themselves when the Ethics Committee votes on the study protocol. A written ICF must be obtained from each subject before inclusion in the study.

12.2 Regulatory Considerations

The study should be conducted in accordance with the ethical principles that have their origin in the *Declaration of Helsinki*, and that are consistent with GCP and the applicable regulatory requirement(s). The investigator or her/his designated representative should promptly submit the protocol to the corresponding Ethics Committee.

A code will be given to each patient instead of his/her name in the study to protect the identity and privacy of patients when reporting AEs and/or other trial-related data.

12.3 Informed Consent

The clinical investigator must explain to the subject that participation in the study is voluntary, that he/she has the right to withdraw at any time and at any stage of the study without discrimination or retaliation, that his/her medical treatment and rights and interests are not affected, and that he/she can continue to receive other treatments. Subjects will be made aware that their participation and personal information used in the study will be treated confidentially. They will also be informed of the nature, purpose, expected potential benefits, potential risks and inconveniences of the study, other available treatment options, and their rights and obligations specified in the *Declaration of Helsinki*, so that they will have sufficient time to consider whether or not they are willing to participate in the study and sign the ICF.

Prior to performance of any protocol-specified procedure, subjects must:

Be informed of the trial-related contents and all contents and terms of the ICF.

Be given sufficient time to ask questions and consider participation.

Voluntarily consent to participate.

Sign and date the ICF approved by the Ethics Committee.

If any update or amendment has been made to the ICF during the study, written informed consent should be obtained from subjects who continue to participate in the study using the updated/revised ICF.

12.4 Protocol Amendments

If the protocol of this clinical study needs to be amended during its actual implementation, the amended study protocol should be submitted to the Ethics Committee for approval before implementation. The investigator should not implement any changes of the protocol without agreement by the sponsor and prior review and documented approval from the Ethics Committee of an amendment except where necessary to eliminate apparent immediate hazards to subjects. Changes to the protocol to eliminate apparent immediate risks to subjects may be implemented immediately but must be documented in the protocol amendment, reported to the Ethics Committee, and submitted to the appropriate regulatory authority within the required period of time.

If significant new findings related to the investigational drug are identified, the ICF must be revised in writing and submitted to the Ethics Committee for approval. Consent of the subjects must be obtained again.

12.5 Study Protocol Deviations

The investigator should record and describe all protocol deviations and timely report those that may affect the subject safety and data integrity to the Ethics Committee and the sponsor as required by the Ethics Committee.

12.6 Study Documentation

The investigator must maintain accurate records to ensure that the conduct of the study is fully documented, including but not limited to, the study protocol, protocol amendments, ICFs, and approval documents from the Ethics Committee and government.

12.7 Termination of the Study

1) Identification of significant safety concerns by the investigator;

2) Demonstration of efficacy that would warrant stopping;

3) Major protocol error leading to inevaluable drug efficacy;

4) Premature discontinuation due to the decision of regulatory authorities.

The termination of the study may be temporary or permanent. When the study is terminated, all study records should be retained for future reference.

12.8 Quality Assurance and Quality Control

The study site should be qualified to conduct a Phase I clinical study, and the facilities and conditions of the department responsible for the project should meet the requirements for safe and effective conduct of the study. Investigators should have expertise, qualifications, and competence to undertake the study and have received training on GCP regulations and on this protocol. Prior to the start of the study, investigators will be trained to be thoroughly familiar with this protocol, and those who pass the performance assessment of protocol training may participate in this study. Investigators participating in the study should be relatively fixed. A new investigator joining halfway as a substitute should receive training, and all participating investigators should have their authorizations updated in a timely manner.

12.9 Study Publication

At the end of the study, the investigator will use appropriate statistical methods to analyze the study data with the assistance of the sponsor and the statistical analysis unit, objectively summarize the study results, objectively evaluate the drug's safety based on the results, and finally make a written final report of the clinical study.

The sponsor and the principal investigator (study site) decide together upon submitting and publishing papers about the study results. The principal investigator should obtain prior written consent from the sponsor when publishing the data obtained from this study, such as in an outside professional society. At the time of publication, the subject information should be kept confidential.

13. REFERENCES

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14. Appendix

Appendix 1. NYHA functional classification system

NYHA classification

Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain

Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain

Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain

Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Objective evaluation criteria

A. No objective evidence of cardiovascular disease

B. Objective evidence of minimal cardiovascular disease

C. Objective evidence of moderately severe cardiovascular disease

D. Objective evidence of severe cardiovascular disease

The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Little, Brown & Co; 1994:254-5

Appendix 2. Grading of hand-foot syndrome (NCI CTCAE v5.0)

Grade 1: Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain

Grade 2: Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental activity of daily living (ADL)

Grade 3: Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL

Appendix 3. Tumor measurement and disease response evaluation: RECIST (version 1.1)

Tumor measurements will be performed on all patients during screening. CT or CT/PET scans of the chest, abdomen/pelvis will be performed to evaluate the tumor as indicated. In addition, enrolled patients with a history of CNS metastases should have a CT or MRI scan of the head at each tumor evaluation.

If these evaluations are not performed during the preceding 2 cycles, they can also be performed at the end of treatment. Subsequent evaluations should use the same imaging method as used during screening.

Anatomical measurements (sum of target lesions) will be recorded during screening and at each subsequent evaluation. The same qualified physician will interpret the results to reduce variability. Radiographic images will be stored at the study site, and examination or test results and investigator's conclusions will be archived in the patient's original documents.

At screening, tumor lesions will be categorized measurable or non-measurable, target or non-target as follows.

Measurable and non-measurable

- **Measurable:** There must be a lesion that can be accurately measured in at least one dimension with a minimum size of 10 mm by CT scan, 10 mm caliper measurement by clinical exam, or 20 mm by chest X-ray; the LD in the plane of measurement should be recorded.
- **Non-measurable:** All other lesions, including small lesions (LD < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions.

Target and non-target

- **Target:** All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be measured and recorded at screening. Target lesions should be selected on the basis of their size (lesions with the LD), but in addition should be those that lend themselves to reproducible accurate measurements. A sum of the LDs for all target lesions will be calculated and recorded on the CRF as the baseline sum of the LDs.
- **Non-target:** All other lesions not classified as target lesions (or sites of disease) should be identified as non-target lesions and recorded on the CRF. Measurements are not required for non-target lesions.

Disease response in target and non-target lesions will be evaluated by the investigator according to the classification and criteria described in Table 36 using RECIST (version 1.1). The best overall response for each patient will be documented as the best response for subsequent objective status using the classification and criteria outlined in Table 37.

Table 3. Response Evaluation Criteria in Solid Tumors (RECIST), a guideline for tumor response evaluation

Tumor response evaluation criteria for target and non-target lesions	
Evaluation of target lesions	
CR:	Disappearance of all target lesions.
PR:	At least a 30% decrease in the sum of the LDs of target lesions, taking as reference the baseline sum of the LDs.
SD:	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the LDs while on study.
PD:	At least a 20% increase in the sum of the LDs of target lesions, taking as reference the smallest sum on study or the appearance of one or more new lesions.
Evaluation of non-target lesions	
CR:	Disappearance of all non-target lesions and normalization of tumor marker level.
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
PD:	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Abbreviation: LD = Longest diameter
Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al.* New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228-47
Website: http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

Table 4. Overall response criteria

Patients with target (+/–non-target) disease			
Target lesions	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
Patients with non-target disease only			
Non-target lesions		**New lesions**	**Overall response**
CR		No	CR
Non-CR/non-PD		No	Non-CR/non-PD
Not all evaluated		No	NE
Unequivocal PD		Yes or No	PD
Any		Yes	PD

Abbreviations: CR: complete response; NE: inevaluable; PD: progressive disease; PR: partial response; SD: stable disease.
Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228-47.
Website: http://www.eortc.be/recist/documents/RECISTGuidelines.pdf