STUDY PROTOCOL

Protocol Number: SARC-IIT-001
Identifier Number: NCT03526679

A Single-arm Phase Ib/II Study of the Combination of **L**envatinib and **E**ribulin in Advanced **Ad**ipocytic Sarcoma and L**e**iomyosa**r**coma

(LEADER study)

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Amendments

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4	Ver 4.0 2021-02-08
5	Ver 5.0 2022-05-10

CONTENT

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
aPTT	activated partial thromboplastin time
Bil	Total bilirubin
CBC	Complete blood count
Ccr	Creatinine clearance
CR	Complete response
Cru	Complete response/unconfirmed
CRF	Case report form
CSF	Cerebrospinal fluid
CT	Computed tomography
D/C	Differential count
DCR	Disease control rate
DOH	Department of Health
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
Gr	Grade
IHC	Immunohistochemical stain
IRB	Institutional Review Board
ITT	Intent to treat
IVF	Intravenous infusion
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCTRC	National Clinical Trial and Research Center,
NS	0.9% Normal saline

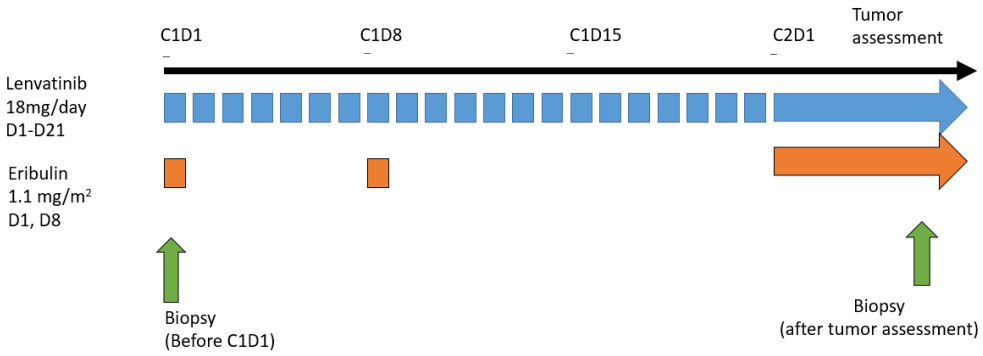
NTUH	National Taiwan University Hospital
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PO	Per os
PR	Partial response
RECIST	Response evaluation criteria in solid tumor
SAE	Serious adverse event
SD	Stable disease
SPD	Sum of the products of the greatest diameter
WBC	White blood cell
WOCBP	Women of childbearing potential
UNL	upper normal limit

Synopsis

Title of Study	A single-arm phase Ib/II study of the combination of **l**envatinib and **e**ribulin in advanced **ad**ipocytic sarcoma and l**e**iomyosa**r**coma (LEADER study)
Rationale of Study	Recently, the US Food and Drug Administration (FDA) granted approval to eribulin for the treatment of adipocytic sarcoma who have received a prior anthracycline-containing regimen based on a Phase III study results of improved overall survival (OS) as compared with the standard treatment dacarbazine. In the leiomyosarcoma cohort of the study, although eribulin did not demonstrate a significant benefit over dacarbazine, still about 5.1% of leiomyosarcoma patients treated with eribulin had a partial response, suggesting that eribulin may have activity against leiomyosarcoma[1]. However, the overall response rate (ORR) and progression-free survival (PFS) remained unsatisfactory in the two most common soft tissue sarcoma (STS) subtypes—adipocytic sarcoma and leiomyosarcoma, prompting new therapeutic options of STS patients. Anti-angiogenic therapies had shown promising results in soft tissue sarcoma (ST). Pazopanib, an anti-angiogenic multi-kinase inhibitor, has shown clinical benefit with a longer median PFS of 4.6 months versus placebo in STS patients refractory to at least one line of systemic chemotherapy[2]. Another anti-angiogenic targeted therapy, regorafenib, showed significant improvement in PFS as compared with placebo in various STS[3]. In a phase I study of lenvatinib for solid tumors in Japan, 4 out of 6 leiomyosarcoma patients has tumor decreased more than 10%[4]. Moreover, other tyrosine receptor targets of lenvatinib, such as fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR), may also plays a role in treating STS. In high-grade STS patients, about 30% of patients had FGFR1 amplification or overexpression. FGFR1-overexpression STS cell lines are sensitive to FGFR inhibitors such as BGJ398 and AZD4547[5]. Furthermore, a monoclonal antibody of PDGFR alpha, olaratumab, was recently approved by the FDA in combination with doxorubicin for advanced STS based on a median 10-month OS benefit compared to doxorubicin only in a randomized phase II trial[6]. It has been demonstrated in various cancer types that an increased

	quantity of tumor infiltrating lymphocyte (TILs) is associated with increased response to chemotherapy or improved prognosis[7]. One of the factors that had been shown to impede the migration and trafficking of TILs into tumor is vascular endothelial growth factor (VEGF)[8]. In renal cell carcinoma, treatment with bevacizumab, an anti-VEGF antibody, or in combination with atezolizumab, increased the recognition of tumor antigen, increased expression of MHC class I receptor on tumor cells, and the amount of TIL migration into the tumor stroma[9]. Many of the STS were detected with scarce TILs in the tumor microenvironment (Chen et al. unpublished data), thus it would be interesting to see if anti-angiogenic tyrosine kinase inhibitors could adjust the tumor microenvironment toward a more chemotherapy-friendly milieu. Thus, we would like to propose a clinical trial to understand the anti-tumor activity of the combination of lenvatinib and eribulin in advanced STS patients.
Objectives and Endpoints	**Primary objective** To evaluate the anti-tumor activity of lenvatinib and eribulin combination in STS. **Primary endpoint for phase Ib** The safety profile of the combination of lenvatinib and eribulin **Primary endpoint for phase II** The objective response rate (ORR) based on RECIST 1.1. **Secondary objectives and endpoints** ● 24-week progression-free survival (PFS) rate ● 6- and 12-months overall survival (OS) rate ● PFS ● OS ● Safety profile of the combination of lenvatinib and eribulin
Study Design	Open-label single arm phase Ib/II study

Schema



Study Treatment:

A 21 day cycle

Table 1: Dose levels of lenvatinib and eribulin combination

Dose level	Lenvatinib	Eribulin
Dose level 11	18mg/day D1-D21	1.1 mg/m^2 D1, D8
Dose level 21	14mg/day D1-D21	1.1 mg/m^2 D1, D8
Dose level 31	10mg/day D1-D21	1.1 mg/m^2 D1, D8
Dose level 12	18mg/day D1-D21	0.7 mg/m^2 D1, D8
Dose level 22	14 mg/da D1-D21	0.7 mg/m^2 D1, D8

The first 6 patients will be treated with lenvatinib 18 mg/day D1-D21 and eribulin 1.1mg/m^2 D1 and D8 (Dose level 11). If no more than 2 (≤ 2) patients had dose-limiting toxicity (DLT) in the first cycle (3 weeks), then the lenvatinib (18) and eribulin (1.1) combination will be declared safe. If more than 2 (> 2) patients have DLT, the investigators will determine which drug is more pertain to the DLT(s) and then will follow the customized block chart to shift the dose. If lenvatinib is determined to be related to DLT, the next lower dose would be dose level 21. Otherwise, if eribulin is determined to be the likely cause for DLT, the next dose level will be level 12. The lowest dose acceptable would be ether dose level 22 or dose level 31. If still more than 2 patients have DLT in the first 6 patients of dose level 22 or level 31, the combination of lenvatinib and eribulin will be considered too toxic in STS patients.

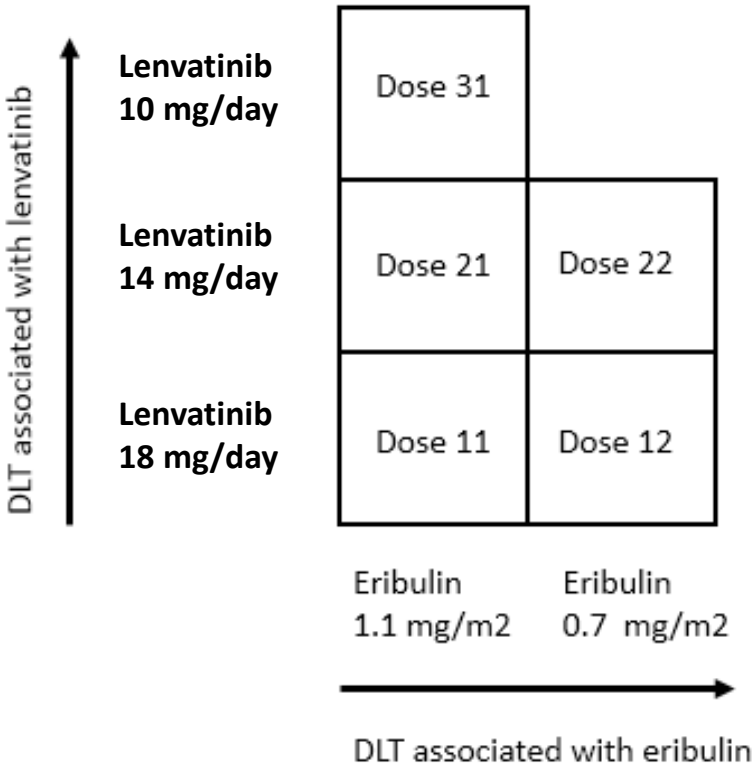
Both agents will be continued until disease progression or intolerable toxicity.

Sample Size (according to primary endpoint)

The study will be based on a minimax Simon 2 stage design. The ORR of interest with lenvatinib and eribulin combination is 20% (P1), and the ORR of low interest is set at 5% (P0). With an 80% power and type I error of 0.05, if no patients had an objective response to lenvatinib

	and eribulin combination after the first 13 enrollments, the trial will be stopped early for futility. If at least one patient had an objective response, the study will continue to include 27 evaluable patients. With an expected 10% drop-out rate, we estimate a total of 30 patients to be enrolled in this study
Study Sites	Single nation, multi-center
Criteria for Inclusion and Exclusion	**Inclusion criteria** To be eligible for inclusion, patients must fulfill the following criteria: 1. A histological confirmed adipocytic sarcoma (dedifferentiated, myxoid, or pleomorphic) or leiomyosarcoma that is either inoperable locally advanced or metastatic 2. Advanced adipocytic sarcoma and leiomyosarcoma who have received no more than 2 lines of systemic chemotherapy in the advanced setting (not including adjuvant chemotherapy). 3. At least one measurable tumor according to RECIST 1.1. If the measurable lesion has previously received radiotherapy, the tumor must be a progressive lesion after radiotherapy. 4. ECOG PS 0 or 1 or Karnofsky performance status (KPS) ≥ 70 5. Patients must have adequate organ function and marrow reserve measured within 14 days prior to randomization as defined below: ■ Hemoglobin ≥ 9.0 g/dL; ■ Absolute neutrophil count ≥ 1,500 / L; ■ Platelets ≥ 75,000/ L; ■ Total bilirubin ≤ 1.5 x upper normal limit; ■ AST(SGOT)/ALT(SGPT) ≤ 2.5 x upper normal limit; for patients with liver metastases AST(SGOT)/ALT(SGPT) ≤ 5 x upper normal limit is allowed; ■ Serum creatinine ≤ 1.5mg/dL or creatinine clearance ≥ 50ml/min; ■ aPTT < 1.5 x upper normal limit (unless on therapeutic anti-coagulation); ■ Proteinuria ≤ 1+ with urine dipstick, if > 1+, 24-hour urine protein must be ≤ 1 g 6. Age 20 or older. 7. Patient's life expectancy is more than 3 months 8. All women of childbearing potential must have a negative pregnancy test obtained within 72 hours before starting

	therapy. 9. Patients with reproductive potential must use effective contraception (hormone or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 6 months after the completion of therapy. 10. Patient needs to have adequate wash-out period from previous systemic treatment(s): (1) 2 weeks for any other oral anti-cancer targeted agents (2) 3 weeks for any other cytotoxic chemotherapy (except for mitomycin-C, which will require 6 weeks) (3) 3 weeks for monoclonal antibodies, including immune checkpoint inhibitors **Exclusion criteria** Patients who fulfill any of the following criteria will be excluded from this trial: 1. Patients who had received lenvatinib or eribulin treatment 2. Patients who had leptomeningeal metastasis, either diagnosed by brain imaging study or confirmed by cerebrospinal fluid cytology examination (patients with brain metastasis that are under control is eligible). 3. Patients with clinical signs or symptoms of gastrointestinal obstruction and who require parenteral hydration and/or nutrition because of obstruction. 4. Patients with uncontrollable hypertension (defined as systolic blood pressure over 140mmHg and/or diastolic pressure over 90mmHg despite anti-hypertensive medications) 5. Patients with the following cardiac disease -Prolongation of corrected QT (QTc) interval to >480 milliseconds (ms). -Significant cardiovascular impairment: history of (a) congestive heart failure greater than New York Heart Association Class II; (b) unstable angina; (c) myocardial infarction; (d) stroke or transient ischemic attack; or (e) cardiac arrhythmia associated with hemodynamic instability within 6 months of the first dose of study drugs. 6. Bleeding subjects at risk for severe hemorrhage.

	7. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to enrollment. 8. History of allergic reaction to compounds of similar chemical composition to the study drugs 9. Pregnancy or lactation. 10. Patients with latent HBV (positive HBsAg or HBeAg) or HCV infection (positive anti-HCV antibody)
Study Medication	Lenvatinib 18mg/day, D1-D21 PO Eribulin 1.1 mg/m^2 D1, D8 IVF Every cycle is 21 days (The above listed dose is the expected dose, but the final starting dose will be determined in the phase Ib part) Figure 1. Dose adjustment directions by DLT  When a safe combination dose is determined, this dose would become the initial dose for the following patients. Dose adjustment for study drugs for adverse events that occur after cycle 1 should follow the protocol guidelines.

	DLT is defined as (1) Grade 4 diarrhea (2) Grade 3 or higher proteinuria (3) Grade 3 or higher hand foot syndrome (4) Grade 3 or 4 peripheral neuropathy (5) Neutropenia Grade 4 that lasted >5 days (6) Neutropenia Grade 3 or 4 complicated by fever and/or infection (Absolute Neutrophil Count [ANC] < 1.0 x 109/L, fever ≥38.5°C) (7) Thrombocytopenia Grade 4 of any duration (8) Thrombocytopenia Grade 3 complicated by bleeding and/or which required platelet or blood transfusion (9) Other Grade 3 or 4 clinically significant non-hematologic toxicities (except for inadequately treated nausea and/or vomiting) considered related to study drug (10) Failure to administer ≥ 75% of the planned dosage of combination therapy as a result of treatment related (at least possibly related) toxicity during Cycle 1. (11) Grade 3 or above hypertension not able to be controlled by medication (12) Grade 3 or above gastrointestinal perforation (13) Grade 4 hemorrhage (14) Grade 3 thromboembolic event (15)Grade 3 or above wound dehiscence requiring medical or surgical intervention
Therapeutic Assessments	1. Therapeutic assessment by CT or MRI will be performed from week 8, 16, and 24 and then every 12 weeks afterwards. A +/- 3 days window is allowed. 2. Biopsy will be performed at baseline and after the first tumor assessment (optional)

Trial Personnel

Principal Investigator

Date
(yyyy/mm/dd)

_____ ____/____/____

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1 Introduction

Background

Recently, the US Food and Drug Administration (FDA) granted approval to eribulin for the treatment of adipocytic sarcoma who have received a prior anthracycline-containing regimen based on a Phase III study results of improved overall survival (OS) as compared with the standard treatment dacarbazine. In the leiomyosarcoma cohort of the study, although eribulin did not demonstrate a significant benefit over dacarbazine, still about 5.1% of leiomyosarcoma patients treated with eribulin had a partial response, suggesting that eribulin may have activity against leiomyosarcoma [1]. However, the overall response rate (ORR) and progression-free survival (PFS) remained unsatisfactory in the two most common soft tissue sarcoma (STS) subtypes—adipocytic sarcoma and leiomyosarcoma, prompting new therapeutic options of STS patients.

Anti-angiogenic therapies had shown promising results in soft tissue sarcoma (ST). Pazopanib, an anti-angiogenic multi-kinase inhibitor, has shown clinical benefit with a longer median PFS of 4.6 months versus placebo in STS patients refractory to at least one line of systemic chemotherapy [2]. Another anti-angiogenic targeted therapy, regorafenib, showed significant improvement in PFS as compared with placebo in various STS [3]. In a phase I study of lenvatinib for solid tumors in Japan, 4 out of 6 leiomyosarcoma patients has tumor decreased more than 10% [4]. Moreover, other tyrosine receptor targets of lenvatinib, such as fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR), may also plays a role in treating STS. In high-grade STS patients, about 30% of patients had FGFR1 amplification or overexpression. FGFR1-overexpression STS cell lines are sensitive to FGFR inhibitors such as BGJ398 and AZD4547 [5]. Furthermore, a monoclonal antibody of PDGFR alpha, olaratumab, was recently approved by the FDA in combination with doxorubicin for advanced STS based on a median 10-month OS benefit compared to doxorubicin only in a randomized phase II trial [6].

It has been demonstrated in various cancer types that an increased quantity of tumor infiltrating lymphocyte (TILs) is associated with increased response to chemotherapy or improved prognosis [7]. One of the factors that had been shown to impede the migration and trafficking of TILs into tumor is vascular endothelial growth factor (VEGF) [8]. In renal cell carcinoma, treatment with bevacizumab, an anti-VEGF antibody, or in combination with atezolizumab, increased the recognition of tumor antigen, increased expression of MHC class I receptor on tumor cells, and the amount of TIL migration into the tumor stroma [9]. Many of the STS were detected with scarce TILs in the tumor microenvironment (Chen et al. unpublished data), thus it would be interesting

to see if anti-angiogenic tyrosine kinase inhibitors could adjust the tumor microenvironment toward a more chemotherapy-friendly milieu.

Thus, we would like to propose a clinical trial to understand the anti-tumor activity of the combination of lenvatinib and eribulin in advanced STS patients.

2 Objectives and Endpoints

Objectives and related endpoints are described in Table 1 below.

Table 1 Objectives and related endpoints

Objectives	**Endpoints**	**Definition and analysis**
Primary (phase Ib)		
To evaluate the safety of lenvatinib and eribulin combination in STS	Dose limiting toxicities (DLT)	Refer to section 5.3
Primary (phase II)		
To evaluate anti-tumor activity of lenvatinib and eribulin combination in STS	Objective Response Rate (ORR)	Refer to Section 7.1
Secondary (phase II)		Refer to Section 7.2
To evaluate the disease control ability of lenvatinib and eribulin in STS	(Progression-free survival) PFS rate at 24- weeks	Refer to Section 7.2.1
	Overall survival rate at 6- and 12-months	Refer to Section 7.2.2
	PFS and OS	Refer to Section 7.2.3
To evaluate the safety dose combination of lenvatinib and eribulin in STS	Incidence, type, intensity, severity and seriousness of Adverse Events (AEs) and frequency of dose interruptions	Refer to section 7.2.4
To evaluate anti-tumor activity of lenvatinib and eribulin combination in STS using other assessment method	Objective Response Rate (ORR) by Choi criteria	Refer to section 7.2.5

3 Patient Selection Criteria

3.1 Inclusion criteria

To be eligible for inclusion, patients must fulfill the following criteria:

1. A histological confirmed adipocytic sarcoma (dedifferentiated, myxoid, or pleomorphic) or leiomyosarcoma that is either inoperable locally advanced or metastatic
2. Advanced adipocytic sarcoma and leiomyosarcoma who have received no more than 2 lines of systemic chemotherapy in the advanced setting (not including adjuvant chemotherapy)
3. At least one measurable tumor according to RECIST 1.1. If the measurable lesion has previously received radiotherapy, the tumor must be a progressive lesion after radiotherapy.
4. ECOG PS 0 or 1 or Karnofsky performance status (KPS) ≥ 70
5. Patients must have adequate organ function and marrow reserve measured within 14 days prior to randomization as defined below:
   - Hemoglobin ≥ 9.0 g/dL;
   - Absolute neutrophil count ≥ 1,500 /μL;
   - Platelets ≥ 75,000/μL;
   - Total bilirubin ≤ 1.5 x upper normal limit;
   - AST(SGOT)/ALT(SGPT) ≤ 2.5 x upper normal limit; for patients with liver metastases AST(SGOT)/ALT(SGPT) ≤ 5 x upper normal limit is allowed;
   - Serum creatinine ≤ 1.5mg/dL or creatinine clearance ≥ 50ml/min;
   - aPTT < 1.5 x upper normal limit (unless on therapeutic anti-coagulation);
   - Proteinuria ≤ 1+ with urine dipstick, if > 1+, 24-hour urine protein must be ≤ 1 g
6. Age 20 or older.
7. Patient's life expectancy is more than 3 months
8. All women of childbearing potential must have a negative pregnancy test obtained within 72 hours before starting therapy.
9. Patients with reproductive potential must use effective contraception (hormone or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 6 months after the completion of therapy.
10. Patient needs to have adequate wash-out period from previous systemic treatment(s):
    (1) 2 weeks for any other oral anti-cancer targeted agents
    (2) 3 weeks for any other cytotoxic chemotherapy (except for mitomycin-C, which will require 6 weeks)
    (3) 3 weeks for monoclonal antibodies, including immune checkpoint inhibitors

3.2 Exclusion criteria

Patients who fulfill any of the following criteria will be excluded from this trial:

1. Patients who had received lenvatinib or eribulin treatment
2. Patients who had leptomeningeal metastasis, either diagnosed by brain imaging

study or confirmed by cerebrospinal fluid cytology examination (patients with brain metastasis that are under control is eligible).

3. Patients with clinical signs or symptoms of gastrointestinal obstruction and who require parenteral hydration and/or nutrition because of obstruction.
4. Patients with uncontrollable hypertension (defined as systolic blood pressure over 140mmHg and/or diastolic pressure over 90mmHg despite anti-hypertensive medications)
5. Patients with the following cardiac disease
   -Prolongation of corrected QT (QTc) interval to >480 milliseconds (ms).
   -Significant cardiovascular impairment: history of
   (a) congestive heart failure greater than New York Heart Association Class II;
   (b) unstable angina;
   (c) myocardial infarction;
   (d) stroke or transient ischemic attack; or
   (e) cardiac arrhythmia associated with hemodynamic instability within 6 months of the first dose of study drugs.
6. Bleeding subjects at risk for severe hemorrhage.
7. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to enrollment.
8. History of allergic reaction to compounds of similar chemical composition to the study drugs
9. Pregnancy or lactation.
10. Patients with latent HBV (positive HBsAg or HBeAg) or HCV infection (positive anti-HCV antibody)

4 Study Design

4.1 Overall plan of the study

This is a single country multi-center, open-label phase Ib/II single-arm study in advanced adipocytic and leiomyosarcoma patients. Patients will be treated with the combination of lenvatinib and eribulin until disease progression, intolerable toxicity, or patient withdrawal.

The first 6 patients will be enrolled in a phase Ib run-in period to evaluated the safety of the combination of lenvatinib and eribulin. If more than 2 patients experience dose-limiting toxicity(s), dose adjustments will be carried out according a pre-determined plan. If there are still more than 2 patients in the lowest pre-specified dose of combination, the combination would be declared too toxic for further treatment in STS patients.

4.2 Study schema

(Please refer to Figure 1)

4.3 Study period and end of study

- Expected recruitment rate: 1 patient/ month
- Expected enrollment duration of the study: 24 months
- Expected follow-up period: 12 months after the last patient accrual.
- Proposed extension of study timeline to 2022/12/13 for complete recruitment, follow-up, and analysis
- Expected total patient accrual: 30 patients
- End of study:
  - This will be a 2-stage study design based on the method proposed by Simon et al. The first stage will recruit 13 patients including 6 patients in the phase Ib part. If 0 patients had any objective response, the study will be unlikely to meet the pre-determined endpoint, and thus will be terminated early. If one or more patients had objective response, a total of 30 patients could be recruited.
  - The study may also terminate early if the combination is too toxic, i.e. that there are more than 2 patients met the DLT criteria in the lowest pre-determined combination dose (detail see Figure 2) in phase Ib part.

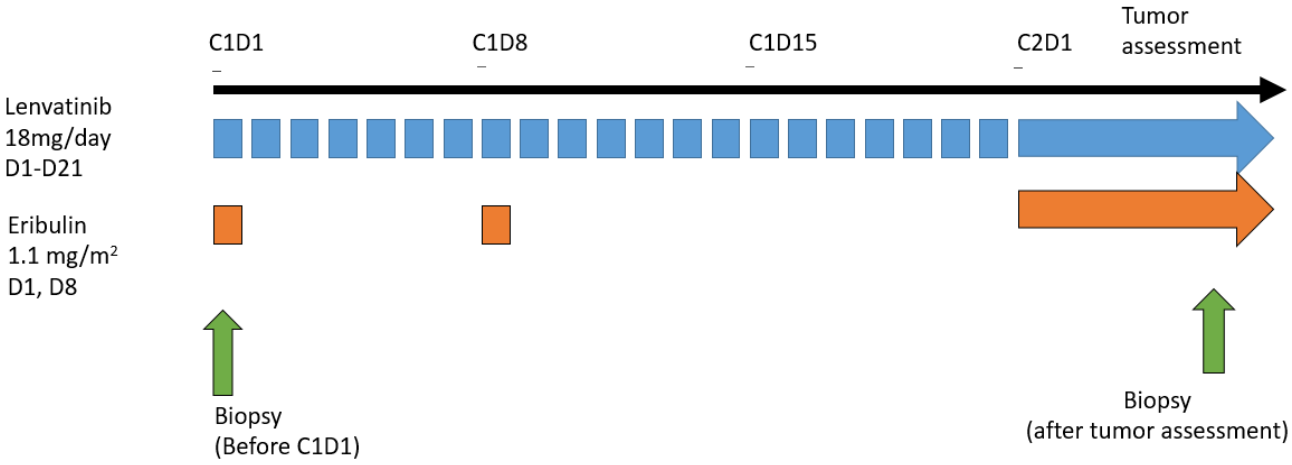

Figure 1. The schema of the study

5 Study Treatment

5.1 Treatment of lenvatinib

Lenvatinib will be given on a once a day daily basis in a 21-day cycle. Lenvatinib will be self-administered by patients orally once a day during the study period. Patients will self-administer lenvatinib at home, except on study visit days. On these visit days, patients should take lenvatinib after chemotherapy is administered. Patients will be instructed to take each dose orally once daily, with or without food, starting on day 1 of

cycle 1. The capsules should be swallowed whole without chewing, dissolving, or opening them. Patients should be instructed to take their dose of study drug at the same time each day. If the usual dosing time is missed, the patient should take the dose that day as soon as they remember as long as this is within 12 hours of the usual time the patient takes the dose. If it has been over 12 hours then this will be considered a missed dose. Patients should not make up missed or vomited doses; dosing should resume on the next calendar day unless otherwise instructed. Patients will be given a medication diary to record all doses taken, missed/skipped, or vomited. This diary will be reviewed with study personnel prior to dispensing medication for the next cycle.

5.2 Treatment eribulin

Eribulin will be given as IV infusion or slowly infusion within 15 or 30 minutes in a 100 or 250ml of 0.9% NaCl solution. Eribulin will be given on days 1 and 8 of every 21-days cycle. Eribulin will be given prior to Lenvatinib administration on days 1 and 8. Each cycle will last 21 (+/- 3) days. Laboratory tests will be performed within 3 days prior to days 1 and 8 of all cycles to assess toxicity and confirm that it is safe to proceed with treatment (see Section 6.5) for a complete listing of assessments). The dose of eribulin will be calculated based on the BSA at study entry and should only be recalculated if there is >10% change in body weight from baseline. The actual body weight will be used for these calculations.

5.2.1 Ancillary and concomitant medications during eribulin treatment

1. Intravenous antihistamine medication and/or steroids could be considered, but not necessary, before eribulin.
2. G-CSF could be administrated subcutaneously or intravenously according to the Taiwan National Health Insurance Policy Guideline. The use of prophylactic G-CSF is at the investigator’s discretion but would not be financially covered by the study.
3. Patients who are taking any herbal (alternative) medicines are NOT eligible for participation.
4. Patients who are undergoing concomitant radiotherapy or chemotherapy are NOT eligible for participation. Radiotherapy is not permitted during study
5. Bisphosphonate or other anti-resorptive agents are acceptable during the study treatment
6. Drug that would lead to QTc prolongation are prohibited during treatment (eg, arrhythmatic drugs such as amiodarone, procainamide; antibiotics such as quinolones and macrolides; antipsychotics drug such as quetiapine, olanzapine, amitriptyline).

5.3 Guidelines combination dose level adjustments in the phase Ib phase

The phase Ib (run-in) phase will be the first 6 patients. This is to monitor the safety of the combination of lenvatinib and eribulin in STS patients. However, this study is not the first study to use the combination of lenvatinib and eribulin in cancer patients. Thus the risk of unexpected DLT may be lower than traditional phase Ib studies. When a safe combination dose is determined, this dose would become the initial dose for the following patients. Dose adjustment for study drugs for adverse events that occur after cycle 1 should follow the protocol guidelines (section 5.4).

5.3.1 Schema for dose adjustments if more than 2 patients have DLT

The first 6 patients will be treated with lenvatinib 18 mg/day D1-D21 and eribulin 1.1 mg/m^2 D1 and D8 (Dose level 11). If no more than 2 (≤ 2) patients had dose-limiting toxicity (DLT) in the first cycle (3 weeks), then the lenvatinib (18) and eribulin (1.1) combination will be declared safe. If more than 2 (> 2) patients have DLT, the investigators will determine which drug is more pertain to the DLT(s) and then will follow the customized block chart to shift the dose. If lenvatinib is determined to be related to DLT, the next lower dose would be dose level 21. Otherwise, if eribulin is determined to be the likely cause for DLT, the next dose level will be level 12. The lowest dose acceptable would be ether dose level 22 or dose level 31. If still more than 2 patients have DLT in the first 6 patients of dose level 22 or level 31, the combination of lenvatinib and eribulin will be considered too toxic in STS patients.

Table 1: dose levels of lenvatinib and eribulin combination

Dose levels*	Lenvatinib	Eribulin
Dose level 11	18mg/day D1-D21	1.1 mg/m^2 D1, D8
Dose level 21	14mg/day D1-D21	1.1 mg/m^2 D1, D8
Dose level 31	10mg/day D1-D21	1.1 mg/m^2 D1, D8
Dose level 12	18mg/day D1-D21	0.7 mg/m^2 D1, D8
Dose level 22	14 mg/da D1-D21	0.7 mg/m^2 D1, D8

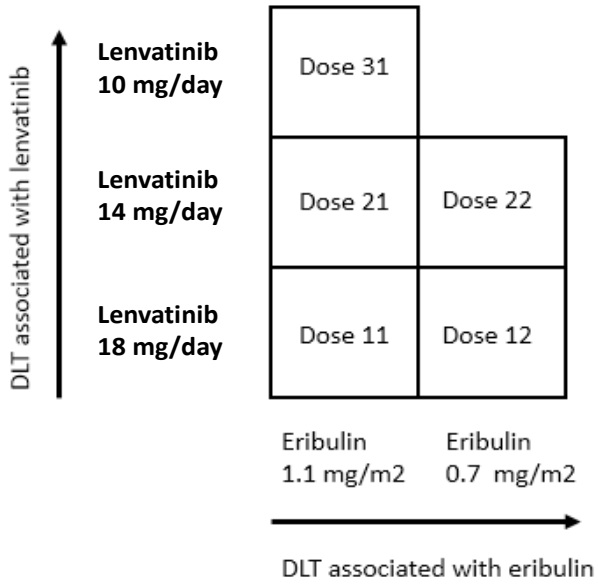

Figure 2. Schematic dose adjustment directions if more than 2 patients have DLT

The Principal Investigator will be responsible to determine the association as to which drug is more likely to be associated with the DLT and the next dose level to be started in the next step of the phase Ib (run-in) phase.

5.3.2 Definitions of DLT

Dose limiting toxicities (DLT) include the following:

(1) Grade 4 diarrhea

(2) Grade 3 or higher proteinuria

(3) Grade 3 or higher hand foot syndrome

(4) Grade 3 or 4 peripheral neuropathy

(5) Neutropenia Grade 4 that lasted >5 days

(6) Neutropenia Grade 3 or 4 complicated by fever and/or infection (Absolute Neutrophil Count [ANC] < 1.0 x 109/L, fever ≥38.5°C)

(7) Thrombocytopenia Grade 4 of any duration

(8) Thrombocytopenia Grade 3 complicated by bleeding and/or which required platelet or blood transfusion

(9) Other Grade 3 or 4 clinically significant non-hematologic toxicities (except for inadequately treated nausea and/or vomiting) considered related to study drug

(10) Failure to administer ≥ 75% of the planned dosage of combination therapy as a result of treatment related (at least possibly related) toxicity during Cycle 1.

(11) Grade 3 or above hypertension not able to be controlled by medication

(12) Grade 3 or above gastrointestinal perforation
(13) Grade 4 hemorrhage
(14) Grade 3 thromboembolic event
(15) Grade 3 or above wound dehiscence requiring medical or surgical intervention

5.3.3 Decision on Final Phase II dose

The final phase II dose will depend on the final result from the phase Ib part, as to which dose level did the phase Ib part confirmed to be safe (Dose 11 or 12 or 21, etc). Patients who received the same dose as to the phase II part will be included into part of the phase II efficacy analysis. (Please also refer to section 10.6 on how two institutions collaborate and determine on this issue)

5.4 Guidelines for dose delays and dose modifications

This part for the guideline is for all phase Ib and phase II patients..
Dose modification is made according to the greatest degree of toxicity that is graded base on Common Terminology Criteria for Adverse Events v4.03 (CTCAE). The CTCAE v4.03 can be downloaded from the CTEP home page. All appropriate treatment areas should have access to a copy of the CTCAE v4.03.
(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

5.4.1 Hematological toxicities

Toxicity	Adverse event	Dose Reduction/Delay	
		Eribulin	Lenvatinib
Hematologic toxicity attributed to any or all treatment	ANC <1000/mm^3 or Platelets 25000-74999/mm^3 within 3 days prior to scheduled therapy	If Day 1: Hold until recovery to ANC >1000/mm^3 and Platelets >75000/mm^3. Resume at same level after recovery If Day 8: Hold until recovery to ANC >1000/mm^3 and Platelets > 75000/mm^3. Resume at same level after recovery	Hold until recovery to ANC > 500/mm^3 and platelets more than 25000/ mm^3, Resume at same level after recovery.
	Platelets <25000/ mm^3 or Platelets 25000-50000/ mm^3 complicated	If Day 1: Hold until recovery to Platelets > 75000/ mm^3. Resume at same level after recovery	Hold until recovery of Platelets 25000/mm^3. Resume at current

	by bleeding, easy bruising, petechiae, or requiring platelet transfusion	If Day 8: Hold until recovery to Platelets > 75000/ mm^3, Resume at same level after recovery	dose level.
	Prolonged neutropenia (ANC<500/ mm^3 for >7 days)	Hold until recovery to ANC>1000/ mm^3. Resume at one dose level below current dose level	Hold until recovery to ANC>500/ mm^3 Resume at same level dose.
	Febrile neutropenia (ANC <1000/ mm^3 with temperature of >38.5^{0}C)	Hold until recovery to ANC>1000/ mm^3. Resume at one dose level below current dose level	Hold until recovery to ANC>1000/ mm^3. Resume at same dose level
	Anemia	No reduction or delay	No reduction of delay

5.4.2 Non-hematological toxicities

Toxicity	Adverse event	Dose Reduction/Delay	
		Eribulin	Lenvatinib
Hepatic toxicities	Grade 3/4 toxicity of AST/ALT/ Total bilirubin	If during treatment there is grade 3/4 liver toxicity then dose reduce by 1 dose level.	Hold until recovery to Grade 1 or baseline. Resume at reduced dose of 14 mg po daily if first occurrence, reduce to 10 mg po daily on second occurrence and 8 mg po daily on third occurrence.
Peripheral neuropathy	Grade 3 or 4	Hold until recover to ≤ grade 2. Reduce dose by one dose level. If neuropathy fails to recover to grade 2 within 3 weeks, eribulin should be discontinued.	No modifications necessary
Nonhematologic toxicity grade 3 or 4 attributed	Grade 3 or 4 nausea/ vomiting despite optimal	Hold until nausea/ vomiting have resolved to	Hold until nausea/ vomiting have resolved to ≤ grade 1. Resume at same

to any or all treatment (except for neuropathy)	antiemetic treatment	≤ grade 1. Resume at same dose level.	dose
	> Grade 2 stomatitis	Hold until stomatitis has resolved to ≤ Grade 1. Resume at one dose level below current dose level	Hold until recovery to ≤ grade 1. Resume at the same dose level
Hypertension	Grade 3 hypertension or life-threatening hypertension	No dose modification necessary	Withhold lenvatinib for Grade 3 hypertension that persists despite optimal antihypertensive therapy; resume at one dose level below current dose level. Discontinue for life-threatening hypertension
Cardiac dysfunction or hemorrhage	Grade 3 or 4 events	No dose modification necessary	Withhold lenvatinib for the development of Grade 3 event until improved to Grade 0 or 1or baseline. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of the adverse event
Proteinuria	Grade 3 or nephrotic syndrome (see footnote)	No dose modification necessary	Withhold lenvatinib until ≤ Grade 2 (proteinuria 2+ or 3+ or 24-hour urinary protein < 3.5g). Resume at next dose below current dose. Discontinue lenvatinib if nephrotic syndrome.
QTc prolongation	Grade 3 or greater	No dose modification necessary	Monitor and correct electrolyte abnormalities in all patients. Withhold lenvatinib for the development of Grade 3 or

			greater QT interval prolongation. Resume lenvatinib at one dose level below the current dose when QTc prolongation resolves to Grade 0 or 1.
Hand foot syndrome	Grade 2	No modification necessary	Withhold until ≤ Grade 1. Resume at the same dose or below current dose at physicians discretion
	Grade 3/4	No modification necessary	Withhold until ≤ Grade 1. May resume at the same dose or below current dose at physicians discretion

- For other grade 3/4 non-hematological toxicities not specifically mentioned in the table: the investigator could decrease the dose of the responsible drug after returning to grade 1 at the physician's discretion.
- If a patient has simultaneous multiple grade 2 adverse events or an intolerable grade 2 adverse events as per CTCAE, the investigator could decrease the dose of the responsible drug after discussion with the Principal Investigator and adjust according to 5.4.3.
- Proteinuria: Grade 2: urine dipstick proteinuria 2+ and 3+; if urine dipstick proteinuria 4+, check 24-hour urine protein, if >= 3.5g/day, confirms grade 3 proteinuria. If <3.5 g/day, follow grade 2 proteinuria schedule

5.4.3 Dose modification or delay durations and modification levels (after phase Ib)

Day 8 dose of eribulin may be delayed for a maximum of 1 week. If toxicities do not improve enough after 1 week delay then omit day 8 dose of eribulin. If day 8 of eribulin is omitted two consecutive cycles eribulin should be resumed at one dose below current dose level.

Eribulin dose modification levels

Dose level 0	1.1mg/m^2
Dose level -1	0.7 mg/m^2

Lenvatinib dose modification levels

Dose level 0	18 mg /day
Dose level -1	14 mg/ day

Dose level -2	10 mg/ day
Dose level -3	8 mg/ day

5.5 Duration of the treatment

- Patients may continue on study therapy until disease progression or until unacceptable toxicity occurs.
- Patients will go off study therapy if any of the following occurs:
  - The patient experiences any grade 4 toxicity after 2 dose modifications, as recommended by the protocol. If treatment is held for 2 consecutive treatment cycles due to toxicity, the patient must go off treatment.
  - The patient withdraws consent from treatment or from the study as a whole.
  - There is disease progression.
  - The treating physician feels it is necessary (e.g. due to patient non-compliance or other safety concerns)

6 Study Assessment/ Procedural Schedule

6.1 Pre-treatment baseline evaluation

Table 6 Assessments necessary before randomization

Investigations		**Timing prior to treatment**
Informed consent		within 28 days
Criteria	All inclusion criteria met All exclusion criteria not met	within 28 days
Medical History	Initial sarcoma AJCC stage Previous chemotherapy and hormonal therapy treatment history Radiotherapy history	within 28 days
Physical Exam	Height, Weight, Blood pressure Karnofsky Performance status Existing symptoms and signs Concurrent medications	within 14 days
Hematology	CBC Differential	within 14 days

	Coagulation	
Biochemistry	Serum creatinine and creatinine clearance[a] BUN Electrolytes (Na, Ca, K, Mg) Albumin Total bilirubin Alkaline phosphatase AST and ALT LDH Urinalysis Serum or urine pregnancy test[b]	within 14 days
Imaging	Chest / Abdominal/pelvis CT scan (or MRI if patient is contraindicated for CT)	within 28 days
Other Investigations	12-Lead ECG	within 14 days
[a] May be calculated using Cockroft-Gault formula. [b] Required for women of childbearing potential only within 72 hours of registration.		

6.2 Pre- treatment assessments

Table 7 Assessments necessary before every cycle of treatment

Investigations		**Timing prior to administration of treatment**
Medical History	Previous treatment toxicity	within 3 days
Physical Exam	Height, Weight, Vital signs Karnofsky performance status Existing symptoms and signs Concurrent medications	within 3 days
Hematology	CBC Differential	within 3 days

Biochemistry	Serum creatinine and creatinine clearance[a] BUN Electrolytes (Na, Ca, K, Mg) Total protein/ Albumin Total bilirubin Alkaline phosphatase AST and ALT LDH Urinalysis	within 3 days
[a] May be calculated using Cockroft-Gault formula.		

6.3 Tumor Assessment during treatment

6.3.1 Tumor imaging criteria—RECIST 1.1

1. The tumor response will be determined by applying **RECIST 1.1.** Assessment schedule of week 8, 16, 24 and every 12 weeks afterwards, according to the regulation of the payment of image study by National Health Insurance. The measurability of a tumor is defined as follows:
   - **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, it can be still be considered as a measurable target according to its clinical course.
   - **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.
   - **Non-measurable lesions** - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and inflammatory breast disease.

   All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

   The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Clinical lesions including skin nodules and palpable lymph nodes will be considered measurable when they are superficial. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

2. Methods of measurement

   CT and MRI are the best and reproducible methods currently available to measure

target lesions selected for response assessment. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

3. Baseline documentation of "Target" and "Non-Target" lesions

All measurable lesions up to a maximum of five lesions in total (maximum two lesions in one organ) should be identified as target lesions and recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

4. Evaluations included following the RECIST 1.1

- Complete response (CR): the disappearance of all known disease, determined by two observations not less than 4 weeks apart.
- Partial response (PR): A 30% or greater decrease in the sum of LD of all lesions in reference to the baseline sum LD. In addition, there may be no appearance of new lesions or progression of any lesion.
- Stable disease (SD): Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR.
- Progressive disease (PD): A 20% or greater increase in the sum of LD of all target lesions, taking as reference the smallest sum LD recorded at or following baseline.
- Once a patient reached PR or CR of his/her tumor assessment, another image will be done 4weeks later. A confirmed PR or CR is defined as both these image tumor assessment is in the same category (PR or CR).

6.3.2 Assessment schedules

- Tumor assessment by CT scan or MRI will be obtained at baseline (as specified in section 6.1), 8 weeks, and 16 weeks and 24 weeks and every 12 weeks afterwards. A +/- 7 days window is acceptable.
- Investigator assessment of the tumor response will be recorded and the investigator will decide treatment plan according to local assessment.

6.3.3 Toxicity assessment

- Each patient will be evaluated for toxicity at baseline, every visit, and as needed at any time during the treatment, based on CTCAE 4.03 criteria.

6.3.4 Follow up of patient status

- Patients with grade 3 or 4 toxicity after treatment will be followed-up until the toxicity resolved to grade 1 or 2.
- All patients will be followed for survival at least 6 months after end-of-treatment. Follow-up interval should be every 8 weeks +/- 1 week.

6.4 Biopsy during the study

- A biopsy of either the primary or metastatic tumor will be taken at baseline (within 4 weeks of initiation of treatment) and after the first tumor assessment. If a disease progression is noted before cycle 3, a biopsy is still suggested.
- Biopsy samples will be used for biomarker testing that included: FGFR pathway analysis and NanoString platform for mRNA analysis of tumor immune microenvironment and biomarker assessment.
- A pre-treatment biopsy will be mandatory for at least 10 patients. If there is a safety concern regarding biopsy, the biopsy could be waived after discussion with the Principal Investigator. The second biopsy will be optional but is strongly suggested.
- A 10ml blood will be drawn +/- 3 days of each biopsy for peripheral blood (PB) analysis and the comparison between PB changes and association with the tumor microenvironment

6.5 Summary Table

Table 8 Flow sheet of LEADER Trial

Study	**Screening**		**L + E Cycle 1 (21 days/cycle)**			**L + E Cycle 2 (21 days/cycle)**			**L+E Cycle 3 and afterwards (21 days/cycle)**			**End of Treatment[i]**
Week	**0**		**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Time window	**-28~0**	**-14~0**	**-3~0**	**-3~0**		**-3 ~ +3 [k]**	**-3 ~ +3 [k]**		**-3 ~ +3 [k]**	**3 ~ +3 [k]**		
Informed consent	X											
Inclusion/ Exclusion criteria	X											
Medical history[b]	X											
Physical examination		X	X	X		X	X		X[j]			X
Performance status (KPS or ECOG)		X	X			X						X
Laboratory assessments												
Hematology (CBC+diff, plts)		X	X	X		X	X		X			X
Serum chemistry[c]		X	X	X		X	X		X			X
Coagulation		X										
Urinalysis		X				X			X			X
Pregnancy test[d]		X	X									
Adverse event assessment[e]		X	X	X	X	X	X	X	X	X	X	X
Tumor assessment[f]		X								X		
12-Lead ECG[g]		X				X			X			X
Biopsy[h]	X (within 4 weeks									X[h]		

L: Lenvatinib, E: eribulin, CBC: complete blood chemistry, ECG: electrocardiogram, KPS: Karnofsky performance status, ECOG: Eastern Cooperative Oncology Group

[a] Medical history, physical examination, vital signs, Karnofsky or ECOG performance status, ECG, adverse events assessment, and concomitant medications may be omitted on Day 1 if these evaluations have been completed within 14 days prior to starting study treatment. Hemogram and biochemistry needs to be repeated within 3 days of Day 1.

[b] History only – survival status, details of recurrent/metastatic disease, new treatments.

[c] Serum creatinine and creatinine clearance, BUN, Electrolytes (Na, Ca, K, Mg), Total protein, Albumin, Alkaline phosphatase, AST and ALT, Total bilirubin, and LDH.

[d] Women of childbearing potential

[e] AEs recorded at every visit, and as needed at any time during the treatment. After end of treatment, AEs will be recorded until 28 days after end of treatment (EOT). The investigator is not required to actively monitor patients for adverse events afterwards. However, the sponsor should be notified if the investigator becomes aware of any post-study serious adverse events or non-serious adverse events of special interest. Other AE reporting details please refer to section 9.3.

[f] Tumor assessment by CT or MRI will be carried out on week 8, week 16, week 24, and every 12 weeks afterwards with a +/- 7 days window. The week 8 and week 24 images will be sponsored by the study and week 16 and images after week 24 will be performed according the National Health Insurance Payment system. If a patient reached CR or PR according to RECIST on the 8-, 16-, or 24-week cycle, a confirmed imaging more than 4 weeks later will be sponsored by the study.

[g] 12-Lead ECG will be performed before every cycle to monitor the QTc for the first 4 cycles, then every 9 weeks afterwards.

[h] The first biopsy will be performed within 4 weeks of treatment starts, the second biopsy will be taken after 1st tumor assessment. At least 10 patients are required to take the pre-treatment biopsy and the second biopsy after treatment is optional but strongly suggested.

[l] Survival follow-up interval is 8 weeks +/- 1 weeks for at least 6 months or death

[J] If in later cycles patient is using only lenvatinib as single agent treatment, D8 visit and blood test could be omitted

[k] two eribulin injections should be at least ≥ 5 days apart

7 Endpoints for Evaluation

7.1 Primary endpoint: Objective response rate (ORR) by RECIST 1.1

- Complete response (CR): the disappearance of all known disease, determined by two observations not less than 4 weeks apart.
- Partial response (PR): A 30% or greater decrease in the sum of LD of all lesions in reference to the baseline sum LD. In addition, there may be no appearance of new lesions or progression of any lesion.
- Stable disease (SD): Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR.
- Progressive disease (PD): A 20% or greater increase in the sum of LD of all target lesions, taking as reference the smallest sum LD recorded at or following baseline.
- Once a patient reached PR or CR of his/her tumor assessment, another image will be done 4weeks later. A confirmed PR or CR is defined as both these image tumor assessment is in the same category (PR or CR).
- An ORR is defined as the either a CR or PR as defined by RECIST 1.1
- The best response as defined by RECIST 1.1 will be used for ORR assessment. The best response is defined as the most proximal response assessment before disease progression. If the first response evaluation showed disease progression, then the best response is PD.

7.2 Secondary endpoints

7.2.1 24-weeks PFS rate

The definition of 24-week PFS rate is the percentage of patients who had **NOT** has an event before or at 24-week after treatment starts. An event is defined as follows:

- Disease progression (PD according to RECIST 1.1)
- Death due to any cause

.

7.2.2 Overall survival (OS) rate at 6- and 12-months

The definition of 6- and 12-months OS rate is the percentage of patients who had **NOT** has an event before or at 6 or 12 months. An event is defined as follows: Death due to any cause.

7.2.3 PFS and OS

PFS is measured from the time of randomization to the time of disease progression (either CNS or extra-CNS, according to RECIST 1.1), or death due to any cause. Patients who have not had an event at the time of data analysis will be censored at the date on which they are

last known to be alive and event-free, on or before the clinical data cutoff date of the respective analysis.
OS is measured from the time of randomization to the time of death. Patients who had not recorded a death event at the time of statistical analysis will be censored at the last time point the patient was known to be alive.

7.2.4 Toxicities assessment

Toxicities will be assessed according to CTCAE 4.03. All grade 3 or 4 toxicities need to be recorded until they resolved to grade 1 or 2.

7.2.5 Choi criteria for objective response rate assessment

Choi criteria are based on changes in tumor size and density following contrast administration on the CT scan. By Choi, radiological PR is defined by the presence of a decrease in tumor size≥10% or a decrease in tumor density/contrast enhancement (CE) on CT scan/MRI≥15%; progression(PD) is defined by the appearance of new lesions or by the increase in tumor, greatest maximal diameter≥10%, without any criteria for PR by tumor density/CE or by increase in tumor density/CE≥15% [11].

8 Statistical Considerations

8.1 Sample size

The study will be based on a minimax Simon 2 stage design. The ORR of interest with lenvatinib and eribulin combination is 20% (P1), and the ORR of low interest is set at 5% (P0). With an 80% power and type I error of 0.05, if no patients had an objective response to lenvatinib and eribulin combination after the first 13 enrollments, the trial will be stopped early for futility. If at least one patient had an objective response, the study will continue to include 27 evaluable patients. With an expected 10% drop-out rate, we estimate a total of 30 patients to be enrolled in this study.
If no dose de-escalation is needed in the phase Ib part, the 6 patients will be considered eligible to be included in the phase II part statistical analysis. If a lower dose is selected as the dose to go forward, only patients with the same dose as the phase II part will be included in the phase II statistical part.

8.2 Statistical analysis

8.2.1 Endpoint estimates

We will provide descriptive statistics and confidence intervals for all variables of interest for which data are collected.

8.3 Correlative science

Objective: to find a predictive biomarker for the combination of eribulin and lenvatinib
Biopsy samples will be acquired for analysis
(1) FGFR pathways will be analyzed by FISH protocol and Sanger sequencing for mutation analysis
(2) mRNA will be purified, test for quality control, and sent for Nanostring nCounter plaform for analyzing the tumor microenvironment
(3) serum biomarkers of immune cytokines and chemokines will be analyzed by Cyokine profiling kits

9 Safety Monitoring and Reporting

9.1 Adverse Events Definition

9.1.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

9.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization. Hospitalization because of disease progression or planned intervention (eg, follow-up imaging, biopsy) are not considered SAE.
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the CRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

9.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study drug is suspected.

9.1.4 Pregnancy

Every patient must be instructed to immediately inform the investigator if she becomes

pregnant during the study. The investigator should report all pregnancies within 24 hours to the sponsor. The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 6 months after the completion of the test “drug” must also be reported to the investigator.

9.1.5 Progression of underlying malignancy

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study. If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

9.2 Relationship to medication

Table 9 AE Relationship to study medication

Unrelated	This category is applicable to those AEs which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, the environment, etc.)
Unlikely	This category is applicable to an AE that does not follow an anticipated response to the trial medication, which may be attributable to something other than the trial medication, and which is more likely to have been produced by the subject’s clinical state or concomitant therapy.
Possible	This category is applicable to an AE that follows a reasonable temporal sequence from administration of the trial medication, that may be an anticipated response to the trial medication, but that could have been produced by the subject’s clinical state or concomitant therapy.
Definite	The category is applicable to an AE that follows an anticipated response to the trial medication, and that is confirmed by both improvement upon stopping the trial medication (de-challenge), and reappearance of the reaction on repeated exposure (re-challenge).

9.3 Reporting adverse events

9.3.1 Adverse events reporting

All adverse events spontaneously reported by the patient or observed by the investigator must be recorded in the CRF. After initiation of protocol treatment, all adverse events, regardless of relationship to study drug, will be reported. AEs will be recorded until 28 days after end of treatment (EOT). After this period, the investigator is not required to actively monitor patients for adverse events; however, the sponsor should be notified if the investigator becomes aware of any post-study serious adverse events.

9.3.2 Immediate reporting requirements from investigator to sponsor and expedited reporting to Health Authority and Ethics Committee/Institutional Review Board

Serious adverse events, non-serious adverse events of special interest, and pregnancies must be reported to Dr. Wei-Wu Chen, Department of Oncology, National Taiwan University Hospital by telephone or email (Tel: 0972652264, Email: tomwchen@ntuh.gov.tw) within 24 hours. The Sponsor will advise the investigator of any further information or documentation that is required. The investigator should also evaluate all serious adverse events and expeditiously report to the Ethics Committee/IRB (Institutional Review Board) according to their requirement and timeline.

9.4 Follow-up after adverse events

Any adverse events greater or higher than grade 3 that are still continuing at the time of one month after last course of protocol treatment final visit must be followed-up until resolution or stabilization, unless in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

All pregnancies reported during the study should be followed until pregnancy outcome is obtained.

10 Administrative and Data Management details

To ensure accurate, complete, and reliable data, the investigator will do the following: Keep records of laboratory tests, clinical notes, and patient's medical records in the patient's files as original source documents for the study.

10.1 Confidentiality

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication. We will code the patients number to, secure the patients CRF in a storage with lockers or computer files with no security breaches.

10.2 Confidentiality of the study subjects

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject

agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor. By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.3 Research budget

(1) CT/ MRI imaging of the first and second assessment (Taiwan's National Health Insurance Bureau will reimburse tumor imaging assessment every 3 months)
30 patients x 2 times = 60 assessments for first 2 assessments at week 8 and 16, respectively. Others including assessments at baseline and after 16 weeks will be covered by NHI insurance.
with multi-parts CT or MRI imaging averaging NTD $20,000 / exam
Total = 20,000 * 2 * 30 = **NTD $1,200,000**

(2) FGFR pathway analysis
FGFR1/chromosome 8 FISH probe
FRS2/chromosome 12 FISH probe
FGFR4 K353 and E550 mutation detection PCR primer
Total = **NTD $ 250,000**

(3) NanoString platform for mRNA analysis of tumor immune microenvironment and biomarker assessment. The NanoString nCounter PanCancer Immune Profiling Panel will be used for analysis
30 patients x 2 biopsies = 60 biomarker samples
with each NanoString analysis = NTD $18,000/ analysis
Total = 18,000 * 60 = **NTD $ 1,080,000**

- The drug will be fully sponsored by Eisai.
- The research personnel (study nurses) will be supported by the Department of Oncology, National Taiwan University Hospital.
- Eisai partially supported with research fund, other parts of the research fund will be supported by intra-mural grant or grants from Clinical Trial Center.

10.4 Publication

Eisai supports the exercise of academic freedom and, subject to the relevant provisions in this Agreement, encourages the Investigator to publish the results of the Study.

- Pre-Publication Review. To ensure against inadvertent disclosure of unprotected Inventions (see Section 10.5, Inventions), the Investigator shall provide Eisai an

opportunity (a minimum of 60 days before submission or other public disclosure) to review any proposed publication, abstract, or other type of disclosure that reports the results of the Study.

- Standards. The Investigator shall comply with all applicable guidelines, recognized ethical standards concerning publications and authorship.
- Disclosure of Support. The Investigator shall disclose Eisai's support of the Study in any publication of Study results.

10.5 Inventions

Any invention or discovery which results from the conduct of the Study and which relates to Study Drug or its use as a treatment or any other Eisai product ("Invention") shall be the exclusive property of Eisai. The Investigator hereby irrevocably assign, and ensure all Study Sites and Research Staff assign, to Eisai (or its nominee) all right, title and interest in all such Inventions, including all intellectual property rights therein, and further agree to assist Eisai and to do all such acts and things as Eisai may advise are necessary or desirable in connection with any such assignment.

10.6 Responsibilities of PIs from participating institutions

Two institutions in Taiwan (National Taiwan University Hospital (NTUH) and Taipei Veterans General Hospital (TVGH)) will participate in the clinical trial. While NTUH and the PI Dr. Wei-Wu Chen is the sponsor of the study, TVGH also plays an integral role in this study. There will be a meeting convened between the two institutions at least every 6 months (can be shorter if one of the PI of each site considers necessary) to discuss and share the observations noted during the course of the clinical trial. However, the meeting will only be convened if the second site (TVGH) has started to enroll patients.

The PI from each institution will be responsible to determine the causative agent for the DLT in the phase Ib part. After 6 patients have completed the phase Ib part, the two PIs from both institutions will also meet together to determine whether it is safe to start the phase II part.
This is a competitive enrollment between two institutions and thus no strict enrolling limits will be set for each institution.

11 Ethical considerations

11.1 General considerations

This study will be conducted in accordance with the ethical principles that have their origin in

the Declaration of Helsinki and will be consistent with Good Clinical Practice (GCP) and applicable regulatory requirements. The study will be conducted in compliance with the protocol. The protocol and any Amendments and the subject informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study. The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

11.2 Informed consent

Freely given written informed consent must be obtained from every subject or their legally acceptable representative (LAR) prior to clinical trial participation, including informed consent for any screening procedures conducted to establish subject eligibility for the trial.

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Appendix I Karnofsky Performance Status scale

Table 1 Karnofsky Performance Status scale definitions rating (%) criteria

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Table 2 Karnofsky Performance Status scale and ECOG scale

Karnofsky	**Scales**	**Zubrod-ECOG-WHO**
Normal, no complaints (常沒有任何抱怨，確定沒有疾病)	100	0 Normal activity fully ambulatory (無症狀)
Able to carry on normal activities, Minor signs or symptoms of disease (可以正常活動，有一些疾病症狀)	90	1 Symptoms, but nearly fully ambulatory (有症狀，完全步行，但對生活無影響)
Normal activity with effort (可以稍微正常活動，已經有一些疾病的症狀)	80	
Cares for self. Unable to carry on normal activity or to do active work (需要自己照顧，無法從事正常活動)	70	2 Some bed time, but needs to be in bed less than 50% of normal daytime (躺在床上的時間<50%) ≦2 分才能接受針劑化學治療
Requires occasional assistance, but able to care for most of his needs (有時需要別人幫助，能照顧患者大部分的需要)	60	
Requires considerable assistance, and frequent medical care(需要考慮別人幫助，經常給予醫療照顧)	50	3 Needs to be in bed more than 50% of normal daytime (躺在床上的時間>50%)
Disabled. Requires special care and assistance (傷殘，需要特別照顧及幫助)	40	
Severely disabled. Hospitalization indicated though death not imminent (嚴重傷殘，尚未有死亡的危險)	30	4 Unable to get out of bed (長期完全臥床)
Very sick. Hospitalization Necessary. Active supportive Treatment necessary (病情嚴重，尚未有死亡的危險)	20	
Moribund (病況緊急，很快有死亡的危險)	10	
Dead	0	5 Dead