A Single-Arm Phase Ib/II Study of Lenvatinib plus Eribulin in Advanced Liposarcoma and Leiomyosarcoma

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ABSTRACT

Purpose: Satisfactory treatment options for advanced leiomyosarcoma and liposarcoma are limited. The LEADER study (NCT03526679) investigated the safety and efficacy of lenvatinib plus eribulin.

Patients and Methods: LEADER is a multicenter phase Ib/II study for advanced leiomyosarcoma or liposarcoma. The phase Ib part enrolled 6 patients to determine the dose-limiting toxicity (DLT) and recommended phase II dose (RP2D) with the starting dose of lenvatinib 18 mg/day and eribulin 1.1 mg/m^2 D1, D8 every 21 days. The primary endpoint of the phase II part was objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors 1.1, with phase Ib patients preplanned to be included in the efficacy analysis. Translational analyses were based on the transcriptomic data obtained from the NanoString nCounter platform.

Results: Thirty patients were enrolled (leiomyosarcoma 21, liposarcoma 9); the median age was 59. One patient had to temporarily stop lenvatinib due to grade 2 arthritis in the first cycle, meeting DLT criteria. Four of 6 patients had to decrease the dose of lenvatinib to 14 mg between cycles two and three. RP2D was determined at lenvatinib 14 mg/day and eribulin 1.1 mg/m^2. The confirmed ORR was 20%, and the ORR was not significantly different between phase Ib/II cohorts ($P = 0.23$). The median progression-free survival was 8.56 months (95% confidence interval, 4.40–not reached). Translational studies suggested increased dendritic cells in the tumor microenvironment (TME) after treatment.

Conclusions: Lenvatinib plus eribulin has a manageable safety profile and exhibits promising efficacy for treating advanced leiomyosarcoma and liposarcoma.

Introduction

Liposarcoma and leiomyosarcoma are the two most common soft-tissue sarcoma (STS) histologic subtypes, and systemic treatment options are limited. Eribulin is a novel anti-microtubule agent with a unique mechanism different from taxanes and vinca alkaloids. In the pivotal phase III study that included advanced liposarcoma and leiomyosarcoma to compare the efficacy of eribulin versus dacarbazine, eribulin was significantly better in terms of its primary endpoint overall survival (OS) with a HR of 0.77 ($P = 0.0169$; ref. 1). Although the FDA approval of eribulin was limited to liposarcoma based on subgroup analysis (2), a separate leiomyosarcoma analysis of the phase III study showed that eribulin has efficacy similar to dacarbazine, an agent considered to be more efficacious in leiomyosarcoma but not in liposarcoma (3). The results, along with other retrospective and real-world studies (4, 5), support the potential of eribulin for leiomyosarcoma treatment.

Antiangiogenic agents and chemotherapy combination improves treatment outcomes in cancer types such as colorectal, lung, and gynecologic cancers (6–9). We hypothesized that adding an antiangiogenic agent to eribulin could improve the outcome of patients with liposarcoma and leiomyosarcoma. Pazopanib is an antiangiogenic agent with an objective response rate (ORR) of 6% and a median progression-free survival (PFS) of 4.6 months in late-line advanced STS (10) but pazopanib and gemcitabine combination has reported inconsistent results (11, 12). Lenvatinib is a novel antiangiogenic small molecular inhibitor that targets FGFRs in addition to vascular endothelial growth factor. In a phase I study of lenvatinib for solid tumors, among the 6 patients with leiomyosarcoma, 1 had a partial response (PR) and 2 had stable disease longer than 6 months (13). In high-grade liposarcoma, phosphorylated and activated FGFR/FRS2 pathway was observed in about 40% of patients. These evidences support exploring the activity of lenvatinib plus eribulin in advanced leiomyosarcoma and liposarcoma (14).

In an era in which immune checkpoint inhibitors have transformed the treatment landscape of oncology, considerable effort has been invested in understanding the immunologic property of nonimmunotherapeutic drugs such as antiangiogenic agents (15, 16). Most STS have low immune cell infiltrates, and the transformation of a suppressive tumor microenvironment (TME) into an active milieu may enhance the efficacy of cytotoxic agents (17–20).

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Translational Relevance

Our study showed that lenvatinib plus eribulin at 14 mg per day and 1.1 mg/m^2 D1, D8 in a 21-day cycle is safe, with manageable side effects, and has promising efficacy in the treatment of advanced leiomyosarcoma and liposarcoma, with an objective response rate of 20% by Response Evaluation Criteria in Solid Tumors 1.1 and a median progression-free survival of 8.56 months. The results provided evidence that combining antiangiogenic agents and chemotherapy is feasible and should be explored in the future. Although with limited translational study specimens, we found evidence suggesting that the combination of lenvatinib and eribulin could potentially change the TME toward a more immune-activated milieu, providing an immunologic perspective on how the combination of lenvatinib plus eribulin could affect the immune cells and cytokines.

In our "A single-arm phase Ib/II study of the combination of lenvatinib and eribulin in advanced adipocytic sarcoma and leiomyosarcoma" (LEADER) study, we aimed to investigate the safety and efficacy of the combination of lenvatinib and eribulin for advanced liposarcoma and leiomyosarcoma. Correlative studies to explore the immunologic manifestations of the combination of lenvatinib and eribulin were designed and incorporated a priori.

Patients and Methods

Study design, treatment, and endpoints

LEADER was a single-arm phase Ib/II study for adult patients with advanced leiomyosarcoma and liposarcoma (excluding well-differentiated liposarcoma) who had received no more than two lines of systemic chemotherapy. The inclusion criteria included: age ≥ 20 years, Eastern Cooperative Oncology Group performance status 0 or 1, and adequate bone marrow and liver and kidney function preservation. Previous treatment with pazopanib was allowed and did not count as a line of chemotherapy in the advanced setting. The trial was registered at clinicaltrials.gov with the identifier NCT03526679.

The study design included two parts: phase Ib and phase II. The primary endpoint for the phase Ib part was safety based on Common Terminology Criteria for Adverse Events 4.0 and recommended phase II dose (RP2D). In the phase Ib part, 6 patients were started with the dose of lenvatinib 18 mg per day and eribulin 1.1 mg/m^2 D1, D8 in a 21-day cycle. Dose-limiting toxicities (DLT) were assessed within the first cycle. Dose adjustment was required if more than 2 patients of the first 6 patients had DLT. However, the protocol stipulated that the decision on RP2D would be based on the overall safety profile of the phase Ib patients (see Supplementary Appendix for criteria for selection of RP2D, the complete list of DLTs, and preplanned dose modification schema).

The primary endpoint of phase II was ORR by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Secondary endpoints included PFS, 6-month PFS rate, and OS. The tumor assessments using CT imaging were performed every 8 weeks in the first 6 months and then every 3 months afterwards.

Clinical trial statistical analysis

The study was based on a minimax Simon two-stage design. The ORR of high and low interest for the combination of lenvatinib and eribulin was 20% (P1) and 5% (P0), respectively. With an 80% power and a type I error of 0.05, if no patients had an objective response after the first 13 enrollments, the trial would be stopped early for futility. If at least 1 patient had an objective response, the study would continue to include 27 evaluable patients. With an expected 10% dropout rate, we planned 30 patients to be enrolled in this study and both phase Ib and phase II patients were preplanned to be included in the efficacy analysis. Although the RP2D of lenvatinib was 14 mg per day, which is lower than the starting dose of 18 mg per day in the phase Ib part (see Results), we decided to perform the primary efficacy analysis as planned because of constraints in expanding patient enrollment. *Ad hoc* analysis to examine the differences in ORR between different lenvatinib starting doses (18 vs. 14 mg per day) were performed by χ^2 test and logistic regression. Other descriptive statistical analyses include median and 95% confidence interval (CI) of PFS and OS, the 6-month PFS rate, and 12-months OS rate.

Trial oversight

The study was performed in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, and the Declaration of Helsinki. The protocol and informed consent documents were approved by the Research Ethics Committee at National Taiwan University Hospital and the Institutional Review Board at Taipei Veterans General Hospital. All participants provided written informed consent.

Biomarker sample preparation

Biopsies were taken from tumors before the start of treatment and before the third cycle of treatment. RNA was extracted from the tumor samples and quantified using the NanoString nCounter PanCancer ImmuneProfile Panel to estimate immune-related molecules. Pretreatment and posttreatment samples were compared in bulk or a paired condition.

Measurement of immune cell abundance

The method of Danaher and colleagues (21) and the Microenvironment Cell Population (MCP)-Counter (22) were used to estimate immune cell population. The immune cell populations assessed using the Danaher-based method included CD8$^+$ T cells, exhausted CD8$^+$ T cells, regulatory T cells, helper T cells, dendritic cells, B cell, mast cells, natural killer cells, natural killer CD56-dim cells, neutrophils, and macrophages. The immune cell populations assessed using the MCP-Counter included T cells, CD8$^+$ T cells, cytotoxic lymphocytes, NK cells, B-lineage cells, monocytic lineage cells, myeloid dendritic cells, neutrophils, and endothelial cells.

Biomarker analysis

The abundance of each immune cell type was tested against clinical efficacy endpoints such as objective response or 6-month PFS rate using the Wilcoxon rank test. Changes in the abundance of different immune cell types in pretreatment and posttreatment samples were also tested using the Wilcoxon rank test. The statistical analyses were performed using R 3.6.3 and associated packages.

Role of the funding source

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Data availability

The data generated in this study are available upon request from the corresponding author.

Results

As of February 28, 2022, 30 patients (female to male, 20:10) had been treated with at least one cycle of lenvatinib plus eribulin (CONSORT Supplementary Fig. S1). Six patients had screen failed. Twenty-one patients had leiomyosarcoma (9 uterine, 12 nonuterine) and 9 had liposarcoma [5 dedifferentiated (DDLPS), 2 myxoid/round cell (MRCLPS), 2 pleomorphic (PleoLPS)]. The median age was 59 years (range, 29–73 years); the median lines of treatment(s) received before enrollment was 1 (range, 0–3). Detailed clinicopathologic characteristics are presented in **Table 1**.

Phase Ib part

Six patients (4 leiomyosarcoma, 1 DDLPS, 1 MRCLPS) started with lenvatinib 18 mg per day and eribulin 1.1 mg/m^2 D1, D8; the median age was 56 (range, 30–70), and 3 (50%) were female. In the 21-day interval of DLT assessment, there was only 1 DLT, which was the failure to administer ≥ 75% of the planned dosage of combination therapy as a result of treatment-related toxicity during Cycle 1. This patient had to hold 1 week of lenvatinib because of grade 2 arthritis. However, within the first 27 cycles of the phase Ib cohort, 4 (67%) patients had late-onset grade 3 toxicities [2 grade 3 hypertension, 1 grade 3 hand–foot syndrome (HFS), 1 grade 3 arthritis] that required dose reduction of lenvatinib. The median time to dose reduction of lenvatinib to 14 mg per day was 29 days (range, 22–43). Thus, taking late toxicities into the consideration, the RP2D was determined at lenvatinib 14 mg per day and eribulin 1.1 mg/m^2 in a 21-day cycle.

Safety

Twenty patients experienced at least one grade 3 or grade 4 adverse event (AE); grade 3 or 4 AEs occurred in > 1 patient and included HFS ($n = 5$), hypertension ($n = 4$), proteinuria ($n = 3$), febrile neutropenia ($n = 3$), and neutropenia ($n = 11$, without prophylactic G-CSF support). Patients treated at RP2D had lower grade 3 HFS (50% vs. 8%, $P = 0.01$) and hypertension (66% vs. 0%, $P = 0.03$) as compared with those treated with the initial starting dose of lenvatinib 18 mg per day. No persistent grade 3/4 AEs for patients receiving long-term treatments were observed. All treatment-emergent AEs ≥ 10% in the phase Ib and II parts, regardless of cause, are presented in **Table 2**.

Table 1. The clinicopathologic characteristics of all patients enrolled into the LEADER study.

Clinical variables	$N = 30$
Female vs. male	20:10
Median age (range)	59 (29–73)
Metastatic vs. locally inoperable	26, 4
Leiomyosarcoma	21
Non-uterine leiomyosarcoma	12
Uterine leiomyosarcoma	9
Liposarcoma	9
DDLPS	5
MRCLPS	2
PleoLPS	2

Prior treatments before enrollment[a]	$N = 30$
Doxorubicin/epirubicin	13
Metronomic cyclophosphamide	6
Pazopanib	5
Ifosfamide	7
Dacarbazine	3
Gemcitabine	3
Docetaxel	2
Trabectedin	1
No prior systemic treatment	11

[a]Only included lines of treatment in the advanced setting.

Efficacy

At the time of last follow-up, 4 patients remained on treatment. All patients (6 and 24 were started with lenvatinib 18 mg and 14 mg per day, respectively) were evaluable for efficacy. The confirmed ORR measured using RECIST 1.1 was 20% (6/30; 95% CI, 8%–39%); this met the primary endpoint criterion. The ORR in leiomyosarcoma and liposarcoma were 19% (4/21, 3 uterine and 1 non-uterine leiomyosarcoma) and 22% (2/9, 1 DDLPS and 1 PleoLPS), respectively. On the basis of the waterfall plot, 77% (23/30) of patients had shrinkage of target lesion/lesions (**Fig. 1A**). A swimmer plot showing the treatment duration of each patient is show in **Fig. 1B**. After a median follow-up time of 25 months, the median PFS and 6-month PFS rate were 8.56 months [95% CI, 4.40–not reached (NR)] and 56%, respectively (**Fig. 2A**). The median PFS times for leiomyosarcoma (8.56 months; 95% CI, 4.17–NR) and liposarcoma (11.36 months; 95% CI, 4.4–NR) were not significantly different ($P = 0.68$). The ORR and median PFS times for those received lenvatinib and eribulin as first-line ($n = 11$) and as second- or later-line treatment ($n = 19$) were 9% (1/11) and 16.0 months and 26% (5/19) and 8.56 months, respectively. The median OS and 12-month OS rate were 27.1 months (95% CI, 21.4–NR) and 89%, respectively (**Fig. 2B**), but patients with liposarcoma had significantly worse OS (median OS leiomyosarcoma vs. liposarcoma: NR vs. 23.6 months, $P = 0.032$). We also examined differences between the efficacy of the 6 patients who started with lenvatinib 18 mg per day (phase Ib, $n = 6$) and those who started with lenvatinib 14 mg per day (phase II, $n = 24$), and the ORRs were not significantly different (2/6 vs. 4/24, $P = 0.23$).

Clinical features that may be associated with clinical efficacy were tested by logistic regression. None of the tested variables, including histology ($P = 0.84$), age ($P = 0.14$), gender ($P = 1.0$), lines of treatment (first line vs. not–first line, $P = 0.27$), and phase (phase Ib vs. phase II, $P = 0.37$), were associated with ORR.

Immune cell–based analysis

A total of 32 samples exhibited adequate RNA quality and quantity for the nCounter platform analysis; 11 patients had paired biopsies. In pretreatment samples, 4 and 15 patients reported PR or nonPR as best response per RECIST 1.1, respectively. In terms of the duration of PFS, 13 patients had PFS ≥ 6 months and 8 patients had PFS < 6 months.

To search for biomarkers potentially associated with clinical outcomes, we compared the pretreatment samples of those with PR ($n = 4$) to those who had nonPR ($n = 15$). We first performed abundance analysis of immune cells. On the basis of the cell types of MCP-Counter, endothelial cells in the TME were the only cell type associated with clinical efficacy (Supplementary Fig. S2). Patients with a higher quantity of endothelial cells had a significantly higher chance of PR ($P = 0.027$). Having a higher quantity of B-lineage cells was also associated with PR ($P = 0.062$; Supplementary Fig. S2). However, none of the immune cell types estimated by the Danaher method were significantly associated with clinical efficacy (Supplementary Fig. S2).

Table 2. Treatment-emergent AEs (regardless of cause) that occurred in ≥ 10% of patients.

AEs	Grade 1		Grade 2		Grade 3		Grade 4		All grades		Grade 3 or 4	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
HFS	6	20.0	11	36.7	5	16.7	0	0.0	22	73.3	5	16.7
AST increase	12	40.0	4	13.3	0	0.0	0	0.0	16	53.3	0	0.0
Neutrophil count decreased	1	3.3	3	10.0	4	13.3	7	23.3	15	50.0	11	36.7
Alopecia	9	30.0	5	16.7	0	0.0	0	0.0	14	46.7	0	0.0
Hypertension	2	6.7	8	26.7	4	13.3	0	0.0	14	46.7	4	13.3
ALT increase	10	33.3	2	6.7	1	3.3	0	0.0	13	43.3	1	3.3
Fatigue	11	36.7	0	0.0	0	0.0	0	0.0	11	36.7	0	0.0
Proteinuria	4	13.3	4	13.3	2	6.7	1	3.3	11	36.7	3	10.0
Diarrhea	5	16.7	3	10.0	1	3.3	0	0.0	9	30.0	1	3.3
Nausea	6	20.0	3	10.0	0	0.0	0	0.0	9	30.0	0	0.0
Fever	6	20.0	1	3.3	0	0.0	0	0.0	7	23.3	0	0.0
Hoarseness	7	23.3	0	0.0	0	0.0	0	0.0	7	23.3	0	0.0
Peripheral sensory neuropathy/numbness	5	16.7	1	3.3	1	3.3	0	0.0	7	23.3	1	3.3
Oral mucositis	5	16.7	1	3.3	0	0.0	0	0.0	6	20.0	0	0.0
WBC decrease	0	0.0	5	16.7	1	3.3	0	0.0	5	16.7	0	0.0
Stomach pain	3	10.0	2	6.7	0	0.0	0	0.0	5	16.7	0	0.0
Gingivitis	4	13.3	1	3.3	0	0.0	0	0.0	5	16.7	0	0.0
Myalgia	3	10.0	1	3.3	1	3.3	0	0.0	5	16.7	1	3.3
Skin rash	1	3.3	3	10.0	1	3.3	0	0.0	5	16.7	1	3.3
Anorexia	0	10.0	3	3.3	1	0.0	0	0.0	4	13.3	0	0.0
Bilirubin increase	0	10.0	3	3.3	1	0.0	0	0.0	4	13.3	0	0.0
Edema	0	10.0	3	3.3	1	0.0	0	0.0	4	13.3	0	0.0
Headache	0	13.3	4	0.0	0	0.0	0	0.0	4	13.3	0	0.0
Muscle soreness	1	0.0	0	10.0	3	3.3	1	0.0	4	13.3	1	3.3
Subclinical hypothyroidism	0	6.7	2	6.7	2	0.0	0	0.0	4	13.3	0	0.0
Abdominal distention	0	3.3	1	6.7	2	0.0	0	0.0	3	10.0	0	0.0
Arthralgia	0	6.7	2	3.3	1	0.0	0	0.0	3	10.0	0	0.0
Anemia	1	0.0	0	6.7	2	3.3	1	0.0	3	10.0	1	3.3
Chest pain	1	0.0	0	6.7	2	3.3	1	0.0	3	10.0	1	3.3
Febrile neutropenia	3	0.0	0	0.0	0	6.7	2	3.3	3	10.0	3	10.0
Platelet decrease	0	3.3	1	6.7	2	0.0	0	0.0	3	10.0	0	0.0
Sore throat	0	6.7	2	3.3	1	0.0	0	0.0	3	10.0	0	0.0

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; WBC, white blood cell.

Pretreatment and posttreatment analysis

The 32 qualified samples consisted of 19 and 13 pretreatment and posttreatment samples, respectively. The posttreatment samples exhibited significantly higher quantities of myeloid dendritic cells (MCP-Counter, $P = 0.037$) and dendritic cells (Danaher method, $P = 0.049$; Supplementary Fig. S3). Similar findings were noted for the 11 paired samples (Danaher dendritic cell increase, $P = 0.032$; MCP-Counter myeloid dendritic cell increase, $P = 0.067$).

Differentially expressed genes

All 730 nonhousekeeping genes in the NanoString PanCancer Immune Profile panel were included for gene-level differential expression (DE) analysis between efficacy endpoints, including RECIST (PR vs. nonPR) and PFS (PFS longer or equal to 6 months vs. PFS shorter than 6 months). On the basis of the pretreatment samples, longer PFS was associated with lower pretreatment *LAG3* level, a marker of exhausted CD8 T cells [longer vs. shorter than 6-month PFS log2 fold change (FC) −1.07, $P = 0.01$). Intriguingly, we also observed that the complement system was associated with the efficacy of lenvatinib plus eribulin. Higher expression of complement genes such as *C1R*, *C1S*, *C3*, *C6*, and *C7* in pretreatment samples was significantly associated with PR or PFS longer than 6 months (Supplementary Fig. S4). Because complement system molecules are not included in either the MCP-Counter or Danaher methods, this finding may be hypothesis-generating and worth further exploration.

We then examined the DE genes between pretreatment and posttreatment samples. The DE genes of the paired samples were mainly associated with dendritic cell regulation. The genes that were significantly upregulated after lenvatinib plus eribulin treatment included *CCL19* (log2FC 1.60, $P = 0.03$) and *TNFSF14* (log2FC 1.13, $P = 0.03$), also known as *LIGHT*. The complete DE genes are listed in Supplementary Table S1.

Discussion

In our LEADER phase Ib/II multicenter study, we demonstrated that the combination of lenvatinib and eribulin could be safely administered at lenvatinib 14 mg per day and eribulin 1.1 mg/m^2 D1, D8 every 21 days. The selection of RP2D based on late toxicities outside the DLT period (first cycle) may be unorthodox but has been widely discussed for molecularly targeted agents (MTA). In an EORTC-led study to investigate optimal methods to determine RP2D for MTA, 50% of patients presented the first grade 3 or higher toxicities of MTA after the first cycle (23). Similarly, 67% of the phase Ib patients in our study appeared with grade 3 AEs associated with lenvatinib after the first cycle. The significant differences in lenvatinib-associated grade 3 AEs (hypertension and HFS) between 14 versus 18 mg per day showed that RP2D selection based on balancing early and late toxicities is feasible without compromising efficacy.

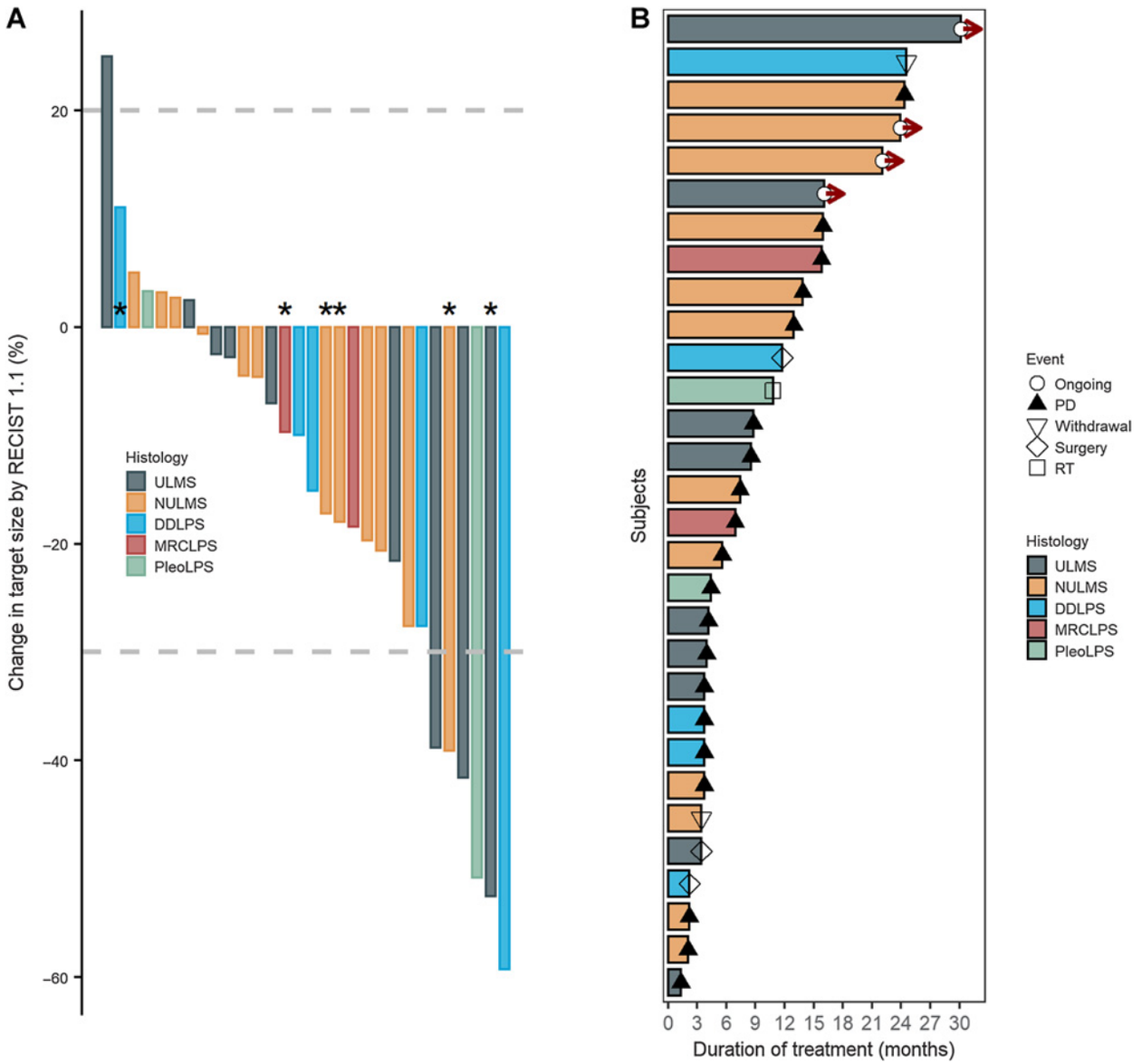

Figure 1.

Efficacy plots. **A,** Waterfall plot showing changes in the target lesion(s) of each patient. Dashed lines indicate the threshold for RECIST criteria of progressive disease (20%) and PR (−30%). Asterisks denotes the patients treated with lenvatinib 18 mg per day at starting phase (phase Ib part). **B,** Swimmer plot showing the duration of treatment. NULMS, non-uterine leiomyosarcoma; PD, disease progression; RT, radiotherapy; ULMS, uterine leiomyosarcoma.

The efficacy results reached our primary endpoint, with ORR based on RECIST 1.1 at 20%. A median PFS of 8.56 months and a 6-month PFS rate of 59% support that the combination is worth further evaluation in advanced STS. These efficacy results were numerically better to those reported for single-agent eribulin in the randomized phase III study with leiomyosarcoma and liposarcoma in the late-line setting where the ORR was 5% and the median PFS was 2.6 months (1). However, cautions need to be emphasized on the differences between these two clinical trials. First, the eribulin randomized phase III study enrolled patients exclusively only in the third- or later-line of treatment while 37% of our patients received the combination as first-line treatment. Secondly, a wide CI (ORR 95% CI, 8%–39%) that inherently comes along with smaller sample size in our study suggest the outcome may not be as robust.

Two clinical trials had reported the efficacy of pazopanib plus gemcitabine in advanced STS. The first is a single-arm study from the French Sarcoma Group that reported an ORR of 24% and a median PFS of 3.8 months in patients with leiomyosarcoma who had failed at least one line of systemic treatment (11). Another randomized study by the German Sarcoma Working Group reported an ORR of 11% and a median PFS of 5.6 months for advanced STS, in which leiomyosarcoma and liposarcoma accounted for 51% of the patients in the pazopanib plus gemcitabine arm (12). In the subgroup of the patients who received lenvatinib

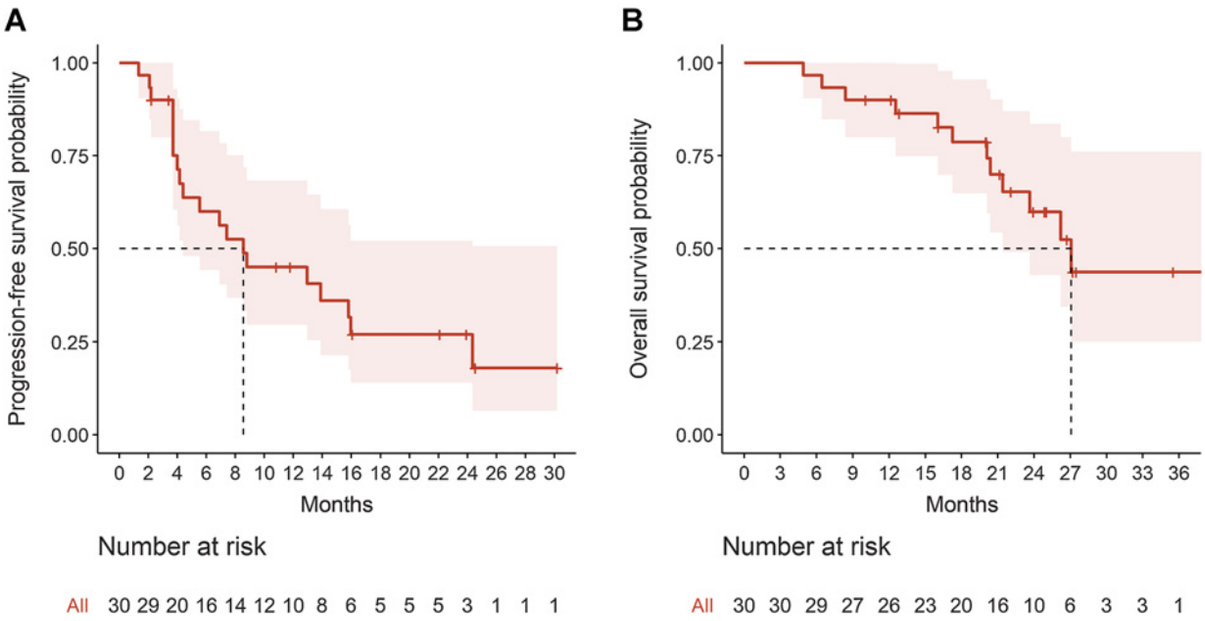

Figure 2.
The efficacy results of the combination of lenvatinib and eribulin. **A,** Kaplan–Meier curve of PFS and 95% CIs. **B,** Kaplan–Meier curve of OS and 95% CIs.

plus eribulin as second- or later-line treatment in our study, the ORR was 26% (5/19) and the median PFS was 8.56 months. Although direct comparison between the studies is impossible and our study has a smaller patient population, lenvatinib plus eribulin showed similar if not better, efficacy in terms of ORR and PFS compared with pazopanib plus gemcitabine in the late-line setting. In terms of AE profile, the differences of grade 3 or higher AEs were mostly due to the different tyrosine kinase inhibitors in the combination, with pazopanib plus gemcitabine having higher grade 3 transaminitis and lenvatinib plus eribulin having higher grade 3 hypertension, HFS, and proteinuria. This AE profiling further signifies the importance of tailoring the dose of MTA when combined with chemotherapy.

Pretreatment and posttreatment samples provide a window for us to investigate the effects of lenvatinib plus eribulin to the TME. Our finding that a higher quantity of endothelial cells was associated with clinical efficacy is consistent with findings from other lenvatinib translational studies (24, 25). However, because of the nature of a combination treatment, we cannot tease out the potential impact of each drug. Eribulin has also shown interesting results in breast cancer that it could decrease angiogenesis (26). More importantly, despite the fact that these two drugs are not typical immunotherapeutic agents, the translational study suggested the combination regimen could potentially transform the TME into a more immunogenic milieu. Both the MCP-Counter and Danaher methods suggested increased dendritic cells and increased expression of chemokines (CCL19 & TNFSF14), indicating rejuvenated dendritic cells (27, 28). The surprising finding that the complement system may be associated with efficacy of lenvatinib plus eribulin is worth further exploration. Complements may stand as a bridge between the innate and adaptive immune systems, and their further exploitation to increase the efficacy of systemic therapy has high potential (29, 30).

The combination of lenvatinib and pembrolizumab has been approved by the FDA for the treatment of advanced renal cell carcinoma (31) and endometrial cancer (32) but has met with challenges in other cancer types such as lung cancer, with no obvious OS benefit of the combination compared with single-agent pembrolizumab in patients with non–small cell lung cancer with PD-L1 tumor-proportion score ≥1% (33). It would be enlightening to understand the role of cytotoxic chemotherapy in modulating the TME. For instance, trabectedin, another cytotoxic chemotherapy approved for liposarcoma and leiomyosarcoma, has been suggested to decrease tumor-associated macrophages in the TME in preclinical model (34). Eribulin not only could decrease angiogenesis in the tumor but also modulate the immunosuppressive cytokine TGFβ (26). Future clinical trials exploring the combination of lenvatinib and eribulin plus another immune checkpoint inhibitor or other immune-modulating agent are worthwhile to expand the treatment options for advanced STS.

Conclusion

In summary, our phase Ib/II LEADER study demonstrated that the combination of lenvatinib and eribulin was associated with tolerable safety and promising efficacy. Translational study results suggested this regimen might modulate the TME.

Authors' Disclosures

T.W.-W. Chen reports grants and personal fees from Eisai and AstraZeneca, as well as personal fees from Roche, Daiichi Sankyo, Bayer, Novartis, Blueprint, Pfizer, and Eli Lilly during the conduct of the study. A.-L. Cheng reports personal fees from F. Hoffmann-La Roche, Chugai Pharmaceutical, Bayer Yakuhin, Novartis, Eisai, Ono Pharmaceutical, Amgen Taiwan, Bristol Myers Squibb, Bayer, Eisai, AstraZeneca, Genentech/Roche, MSD, BeiGene, Exelixis, Ipsen Innovation, and IQVIA outside the submitted work. C.-C. Yen reports grants from National Science and Technology Council of Taiwan and Taipei Veterans General Hospital during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

T.W.-W. Chen: Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and

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Note

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