Dose Escalation Data from the Phase 1 Study of the Liposomal Formulation of Eribulin (E7389-LF) in Japanese Patients with Advanced Solid Tumors

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ABSTRACT

Purpose: We report the dose-escalation part of a phase I study of liposomal eribulin (E7389-LF) in Japanese patients with advanced solid tumors and no alternative standard therapy.

Patients and Methods: Patients ≥20 years old were enrolled. E7389-LF doses of 1.0 to 1.5 mg/m^2 once every two weeks (Q2W) or 1.0 to 2.5 mg/m^2 once every three weeks (Q3W) were planned. The primary objective was to determine the MTD by evaluating dose-limiting toxicities (DLT). Secondary objectives included safety/tolerability assessments, objective response rate (ORR), and progression-free survival; serum biomarker assessment was an exploratory objective.

Results: Twenty-one patients were enrolled and treated; 12 in the Q3W group (1.0 mg/m^2, $n = 3$; 1.5 mg/m^2, $n = 3$; 2.0 mg/m^2, $n = 6$) and 9 in the Q2W group (1.0 mg/m^2, n=3; 1.5 mg/m^2, $n = 6$). The Q3W and Q2W MTDs were 2.0 mg/m^2 and 1.5 mg/m^2, respectively. One patient receiving 2.0 mg/m^2 Q3W had a DLT of grade 3 febrile neutropenia. The most common grade 3 treatment-emergent adverse events were neutropenia (66.7% in Q3W and Q2W) and leukopenia (Q3W, 58.3%; Q2W, 33.3%). One patient in the Q3W group (2.0 mg/m^2) and 3 in the Q2W group (1.0 mg/m^2, $n = 1$; 1.5 mg/m^2, $n = 2$) achieved a partial response [overall ORR, 19.0%; 95% confidence interval (CI), 5.4–41.9]. Endothelial [TEK receptor tyrosine kinase (TEK), intercellular adhesion molecule 1 (ICAM1), vascular endothelial growth factor receptor 3 (VEGFR3), platelet/endothelial cell adhesion molecule 1 (PECAM1)], vasculature (collagen IV), and immune-related [interferon gamma (IFNγ), C-X-C motif chemokine ligand 11 (CXCL11), C-X-C motif chemokine ligand 10 (CXCL10)] biomarker levels were increased.

Conclusions: E7389-LF was well tolerated at 2.0 mg/m^2 Q3W and 1.5 mg/m^2 Q2W. Considering the toxicity profile of both regimens, the recommended dose was 2.0 mg/m^2 Q3W. Expansion cohorts are ongoing.

Introduction

Eribulin is a halichondrin-class microtubule dynamics inhibitor with a distinct binding profile that has demonstrated antitumor activity in several advanced solid tumors, including breast cancer and soft tissue sarcoma (1). In addition to eribulin's effects on microtubule dynamics, nonclinical studies have identified unique actions on the tumor microenvironment such as increasing vascular perfusion and permeability in tumor cores, promoting the epithelial state, and reducing the capacity of breast cancer cells to migrate (2, 3).

Eribulin is approved (as eribulin mesylate) for the treatment of inoperable or recurrent breast cancer in Japan (4), metastatic breast cancer after ≥2 prior lines of chemotherapy in the United States (5), and locally advanced or metastatic breast cancer after ≥1 prior line of chemotherapy in Europe (6). In addition, eribulin is approved for the treatment of soft-tissue sarcoma in Japan (4), unresectable or metastatic liposarcoma after anthracycline therapy in the United States (5), and unresectable liposarcoma after anthracycline therapy in Europe (6). Despite eribulin's antitumor activities, hematologic adverse events (its major toxicity) frequently lead to dose reduction (5). Recent development of a liposomal drug delivery system is expected to improve systemic toxicity of eribulin.

Liposomes are spherical vesicles that encase drugs within a phospholipid or other amphiphilic bilayer (7). This encapsulation can facilitate drug transportation throughout the body by protecting the

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Translational Relevance

This phase I study assessed the tolerability and efficacy of a liposomal formulation of eribulin (E7389-LF) in patients with advanced solid tumors. This formulation was intended to reduce the toxicity of eribulin by facilitating transportation into tumors. Of the 21 patients, 4 achieved a partial response for a response rate of 19%. E7389-LF was well tolerated overall; occurrences of dose interruption and discontinuation due to treatment-emergent adverse events were minimal. Further, endothelial cell, vasculature, and immune-related biomarkers were increased after treatment. Thus, eribulin may influence tumor vascular remodeling by increasing endothelial, vasculature, and immune-related cell markers. This study supports the further development of E7389-LF for treating a range of advanced solid tumors. Particularly, expansion cohorts are ongoing to evaluate efficacy in specific tumor types.

drug from inactivation or dilution while in circulation and increasing the therapeutic index by reducing accumulation in tissues at risk for toxicity (8). Of particular relevance to cancer treatment, liposomes have also been shown to accumulate in tumors via an enhanced permeability and retention effect (8). This novel drug delivery system could enhance eribulin's efficacy and reduce systemic toxicity.

A liposomal formulation of eribulin (E7389-LF) was developed to potentially expand its therapeutic profile (9), as encapsulation within liposomes may help anticancer drugs accumulate within tumor tissue by exploiting the vascular permeability and immature lymphatic structure of tumors (10). As eribulin has been shown to increase the accumulation of liposomes via an enhanced permeability and retention effect (11), E7389-LF may also induce vascular remodeling. In a first-in-human study of patients with advanced solid tumors conducted in the United Kingdom, the MTD [defined as the maximum dose with 0–1 dose-limiting toxicities (DLT) in 6 patients] of E7389-LF was 1.4 mg/m^2 every 3 weeks (Q3W) or 1.5 mg/m^2 every 2 weeks (Q2W; ref. 12). Observed DLTs included increased aspartate aminotransferase (AST) levels, increased alanine aminotransferase (ALT) levels, neutropenia, febrile neutropenia, stomatitis, and hypophosphatemia. We conducted this phase I study to evaluate safety and tolerability of E7389-LF in Japanese patients with advanced, unresectable, or recurrent solid tumors and reassess the MTD of both the Q2W and Q3W schedules.

Patients and Methods

Study design

This was the dose-escalation part of a phase I open-label study to evaluate the safety and tolerability of intravenous E7389-LF in Japanese patients with advanced, unresectable, or recurrent solid tumors for which no alternative standard therapy or effective therapy exists. The MTD of E7389-LF was evaluated using a standard "3 + 3" design dose-escalation method of two treatment schedules assessed in parallel. E7389-LF was dosed by eribulin free base content, and was administered either Q3W (on day 1 of a 21-day cycle) or Q2W (on days 1 and 15 of a 28-day cycle). The initial dose level of E7389-LF was 1.0 mg/m^2 for both schedules, as it was well tolerated with no DLTs in an early analysis of the first-in-human trial (12). The upper dose level of the Q2W dosing group was set at 1.5 mg/m^2, also based on the previous first-in-human study (12). The upper dose level of the Q3W dosing group was set at 2.5 mg/m^2, considering a similar maximum planned dose intensity to the Q2W group (0.75 mg/m^2/week), which was higher than the Q3W group in the first-in-human study (12). Prophylactic administration of granulocyte colony-stimulating factor was not permitted during cycle 1, but was permitted after cycle 2 and after considering the hematologic adverse events.

This study was conducted in accordance with standard operating procedures of the sponsor, which were based on the Principles of the World Medical Association Declaration of Helsinki, all applicable Japanese Good Clinical Practices and regulations, and the Pharmaceutical and Medical Device Act for studies conducted in Japan. Written informed consent forms were obtained from all participants; these and the study protocol were reviewed and approved by the applicable institutional ethical review board.

Patients

The study enrolled Japanese patients aged ≥20 years with advanced, unresectable, or recurrent solid tumors for which no alternative standard therapy or no effective therapy existed. Additional inclusion criteria were a life expectancy ≥12 weeks, an Eastern Cooperative Oncology Group performance status of 0 or 1, and an adequate washout period before study drug administration. Patients were excluded if they had received prior eribulin treatment, had a history of hypersensitivity reaction from a liposomal formulation agent, active viral hepatitis (B or C) as demonstrated by positive serology or requiring treatment, or were human immunodeficiency virus positive.

Study objectives and assessments

The primary objective was to determine the MTD of E7389-LF. DLTs were defined as treatment-related adverse events occurring during cycle 1 of the dose-escalation part of the study. These were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (13). Definitions of DLTs included grade 3 to 4 febrile neutropenia, grade 4 neutropenia lasting ≥8 days despite optimal treatment, grade 4 thrombocytopenia, drug hypersensitivity event (grade 4, or grade 3 unresolved within 24 hours or recurring with same severity, despite treatment), and other clinically significant grade ≥3 nonhematologic events and abnormal laboratory toxicities.

Secondary objectives were to assess the safety and tolerability, pharmacokinetic (PK) profile, objective response rate (ORR), and progression-free survival (PFS) of E7389-LF. Exploratory objectives included assessment of disease control rate (DCR), clinical benefit rate (CBR), and serum biomarkers.

Serum biomarker analyses were conducted to evaluate the effect of E7389-LF on endothelial cell markers, vasculature markers, and immune-related markers. Serum samples were collected at baseline, on day 1 of cycles 1 through 6, and at the discontinuation visit (14–42 days after last administration of E7389-LF). The serum biomarker assay was performed on serum samples using multiplex or Simoa methodology for 81 analytes. Serum samples were analyzed at pretreatment on cycle 1 day 1 (C1D1), and before subsequent doses on C2D1, C3D1, and C4D1. Data below the lower quantification limit (QL) for serum biomarkers were defined as out of range and replaced by half of the lower QL. Serum pharmacodynamic biomarker analyses were performed for analytes when less than 20% of their measurements were below the lower QL.

Statistical analysis

The sample size was not based on statistical powering, rather the design of the dose-escalation part was based on traditional 3 + 3

patients per cohort with multiple planned dose levels. All efficacy and safety analyses were performed on the safety analysis set, which includes all patients who received at least one dose of study drug. Best overall response was evaluated according to RECIST version 1.1 criteria (14). ORR, DCR [complete response (CR) + partial response (PR) + stable disease (SD); duration of ≥5 weeks after C1D1], and CBR (CR + PR + SD; duration of ≥23 weeks after C1D1) were provided with 95% confidence interval (CI) according to the Clopper–Pearson method.

The PK analysis was performed in all patients who received at least one dose of study drug and had at least one evaluable plasma concentration. Blood samples for the assessment were collected before and after administration of E7389-LF C1D1 doses as follows: predose; at 15 minutes after the start of infusion; at 5 minutes and 0.5, 1, 2, 4, 6, 8, and 24 hours after the end of infusion; and then at C1D4, C1D8, and C1D10. Both total eribulin (encapsulated and released eribulin in both plasma protein bound and unbound forms) and free eribulin (released from liposomes and plasma protein unbound form) were measured using a validated LC/MS-MS method. Ultrafiltration method was used to obtain samples to measure concentrations of free eribulin.

PK parameters were calculated for total and free eribulin by noncompartmental analysis using actual sampling times. PK parameters include maximum plasma concentration (C_{max}), time at which the C_{max} occurs (t_{max}), area under the plasma concentration–time curve (AUC) for both total and free eribulin, and terminal elimination phase half-life ($t_{½}$), total clearance (CL), and volume of distribution at steady state (V_{ss}) for total eribulin only. Because PK parameters were derived from plasma concentration data only after first administration of E7389-LF, they were summarized by combining the individual data from both the Q2W and the Q3W dosing groups by dose level.

Serum biomarker analyses included all patients who received at least one dose of study drug and had evaluable biomarker data.

Statistical analyses and plots for biomarkers were performed and generated using R (R Foundation for Statistical Computing) version 3.6.3. Pharmacodynamic changes of serum biomarkers from baseline (or C1D1) were analyzed using the one-sample Wilcoxon signed-rank test, and *P* values were adjusted using the Benjamini–Hochberg procedure for false discovery rate control with the number of biomarkers analyzed at each time point. Statistical significance was determined when the unadjusted *P* values were < 0.05.

Data availability

Eisai Inc. commits to sharing data from clinical trials upon request from qualified scientific and medical researchers. Data requests are reviewed and authorized by an independent review panel on the basis of scientific merit, and data is anonymized with respect to applicable laws and regulations. Trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

Results

Patients

From August 2017 to May 2018, 21 patients were enrolled and treated. Analyses were completed prior to database lock; data as of June 2020 was used for the dose-escalation analysis, at which point all patients discontinued the study. Twelve patients were in the E7389-LF Q3W dosing group (3 at a dose of 1.0 mg/m^2, 3 at 1.5 mg/m^2, and 6 at 2.0 mg/m^2) and 9 patients in the Q2W dosing group (3 at a dose of 1.0 mg/m^2 and 6 at 1.5 mg/m^2). Patient characteristics are described in **Table 1** and Supplementary Fig. S1. These were generally similar between the Q3W and Q2W dosing groups, except for the male to female ratio and number of prior chemotherapy regimens. In the Q3W dosing group, 41.7% of patients were male and 8.3% of patients had received fewer than 2 prior chemotherapy regimens; in the Q2W dosing group, 55.6% of patients were male, and 44.4% of patients had received fewer than 2 prior chemotherapy regimens.

MTD

The E7389-LF Q3W and Q2W group MTDs were determined to be 2.0 mg/m^2 and 1.5 mg/m^2, respectively. There was one patient in the Q3W dosing group (2.0 mg/m^2) who experienced a DLT (grade 3 febrile neutropenia, from which the patient recovered). There were no DLTs observed in the Q2W dosing group.

Table 1. Baseline patient characteristics.

Characteristics	E7389-LF Q3W total (*n* = 12)	E7389-LF Q2W total (*n* = 9)	Overall (*N* = 21)
Median age, years (range)	51.5 (22–68)	59.0 (28–68)	58.0 (22–68)
Sex, *n* (%)			
Male	5 (41.7)	5 (55.6)	10 (47.6)
Female	7 (58.3)	4 (44.4)	11 (52.4)
ECOG performance status, *n* (%)			
0	6 (50.0)	5 (55.6)	11 (52.4)
1	6 (50.0)	4 (44.4)	10 (47.6)
Median body surface area, m^2 (range)	1.5 (1.3–1.9)	1.6 (1.4–2.4)	1.6 (1.3–2.4)
Number of prior anticancer therapy regimens, *n* (%)			
<2	1 (8.3)	4 (44.4)	5 (23.8)
2–4	10 (83.3)	4 (44.4)	14 (66.7)
≥5	1 (8.3)	1 (11.1)	2 (9.5)

Note: Percentages are based on the total number of patients in the safety analysis set within the relevant treatment group. Prior therapy excludes radiotherapy and surgery.
Abbreviations: E7389-LF, eribulin liposomal formulation; ECOG, Eastern Cooperative Oncology Group; Q2W, every 2 weeks; Q3W, every 3 weeks.

Table 2. Safety summary.

Parameters	E7389-LF Q3W				E7389-LF Q2W		
	1.0 mg/m^2 (n = 3)	1.5 mg/m^2 (n = 3)	2.0 mg/m^2 (n = 6)	Total (n = 12)	1.0 mg/m^2 (n = 3)	1.5 mg/m^2 (n = 6)	Total (n = 9)
Median duration of treatment, months[a]	1.38	1.38	3.12	2.78	2.83	5.59	2.89
Range	1.4–9.7	1.4–13.2	1.4–25.5	1.4–25.5	1.8–15.6	0.9–13.8	0.9–15.6
Any TEAEs, n (%)	3 (100)	3 (100)	6 (100)[b]	12 (100)	3 (100)	6 (100)	9 (100)
Grade 1	1 (33.3)	0	0	1 (8.3)	1 (33.3)	0	1 (11.1)
Grade 2	1 (33.3)	0	1 (16.7)	2 (16.7)	0	0	0
Grade 3	1 (33.3)	0	0	1 (8.3)	2 (66.7)	2 (33.3)	4 (44.4)
Grade 4	0	3 (100)	4 (66.7)	7 (58.3)	0	4 (66.7)	4 (44.4)
SAEs, n (%)[c]	0	1 (33.3)	2 (33.3)	3 (25.0)	0	1 (16.7)	1 (11.1)
Upper limb fracture	0	0	1 (16.7)	1 (8.3)	0	0	0
Hematuria	0	0	0	0	0	1 (16.7)	1 (11.1)
Hemoptysis	0	1 (33.3)	0	1 (8.3)	0	0	0
Respiratory failure	0	0	1 (16.7)	1 (8.3)	0	0	0
Treatment-related TEAEs, n (%)	3 (100)	3 (100)	6 (100)	12 (100)	2 (66.7)	6 (100)	8 (88.9)
Grade 1	1 (33.3)	0	0	1 (8.3)	0	0	0
Grade 2	1 (33.3)	0	1 (16.7)	2 (16.7)	1 (33.3)	0	1 (11.1)
Grade 3	1 (33.3)	0	0	1 (8.3)	1 (33.3)	2 (33.3)	3 (33.3)
Grade 4	0	3 (100)	5 (83.3)	8 (66.7)	0	4 (66.7)	4 (44.4)

Note: Percentages are based on the total number of patients in the safety analysis set within the relevant treatment group. A patient with two or more adverse events in the same preferred term was counted only once for that preferred term. Adverse-event terms were coded using the Medical Dictionary for Regulatory Activities version 23.1. Adverse events were graded using CTCAE version 4.03. Treatment-related TEAEs include TEAEs with missing causality and TEAEs that were considered by the investigator to have a reasonable possibility of relation to the study drug.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; E7389-LF, eribulin liposomal formulation; Q2W, every 2 weeks; Q3W, every 3 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]Duration of Q3W treatment = (date of day 1 of final cycle + 21 – date of first dose)/(365.25/12). Duration of Q2W treatment = (date of day 1 of final cycle + 28 – date of first dose)/(365.25/12).

[b]One grade 5 TEAE of respiratory failure was also reported.

[c]All SAEs were unrelated to study drug except for hemoptysis, and all were rated as grade 3 except for respiratory failure, which was grade 5.

Safety

The median duration of treatment was 2.78 months (range 1.4−25.5) and 2.89 months (range 0.9−15.6) in the E7389-LF Q3W and Q2W dosing groups, respectively (**Table 2**).

All patients experienced treatment-emergent adverse events (TEAEs) in both the Q3W (n = 12) and Q2W (n = 9) dosing groups (**Table 2**). The most common grade ≥3 TEAEs were neutropenia (66.7% in both groups) and leukopenia (58.3% in Q3W group; 33.3% in Q2W group); TEAEs for grades 1 to 4 are shown in **Table 3**. The nadir of the neutrophil count occurred during days 8 to 15 for both groups (Supplementary Fig. S2).

Serious adverse events (SAEs) unrelated to study drug occurred in 2 patients in the Q3W dosing group [grade 3 upper limb fracture (n = 1), and grade 5 respiratory failure due to disease progression in a patient with lung tumor lesions (n = 1)] and 1 patient in the Q2W dosing group (grade 3 hematuria due to disease progression in a recurrent primary bladder tumor lesion). Grade 3 hemoptysis related to study drug occurred in 1 patient in the Q3W dosing group. TEAEs led to dose reductions in 3 patients (25.0%) in the Q3W dosing group [grade 4 neutropenia (n = 1), grade 3 anemia (n = 1), and grade 3 febrile neutropenia (n = 1)] and 4 patients (44.4%) in the Q2W dosing group [grade 3 neutropenia (n = 3), grade 3 angina pectoris (n = 1), and grade 3 peripheral sensory neuropathy (n = 1)]. TEAEs led to dose interruptions in 0 patients in the Q3W dosing group, and 2 patients (22.2%) within the Q2W dosing group [grade 2 laryngitis (n = 1) and grade 2 pneumonia (n = 1)]. TEAEs led to study-drug discontinuation in 1 patient (8.3%; grade 4 thrombocytopenia) within the Q3W dosing group. There were no patients who discontinued treatment due to TEAEs in the Q2W dosing group. Overall, the most common toxicities (Q3W/Q2W groups) included neutropenia (83.3%/88.9%), leukopenia (83.3%/77.8%), nausea (83.3%/22.2%), and increases in AST level (58.3%/55.6%) and ALT (50.0%/55.6%) level. Two hypersensitivity reactions occurred: one in the Q3W group, and one in the Q2W group.

Efficacy

In the overall population, 4 patients achieved PR for an ORR of 19.0% (95% CI, 5.4−41.9; Supplementary Table S1). These four cancer types were adenoid cystic carcinoma (ACC), esophageal cancer, urothelial cancer, and uterine small cell cancer (Supplementary Fig. S1). Three of the responses were in the E7389-LF Q2W group (1.5 mg/m^2, n = 2; 1.0 mg/m^2, n = 1), while the remaining responder was taking E7389-LF 2.0 mg/m^2 Q3W. The CBR was also somewhat higher in the Q2W regimens (55.6%) than the Q3W regimens (33.3%), although the overall DCR was 66.7% for either regimen frequency. The percentage change in the sum of tumor diameters from baseline over time is shown in **Fig. 1**. Median PFS was 2.8 months in the overall population and in both the Q2W and Q3W regimens. The maximum percentage change in the sum of tumor diameters from baseline is shown in Supplementary Fig. S3.

PK analyses

Plasma concentration of total eribulin after single administration of E7389-LF was substantially greater than that after administration of commercially available eribulin mesylate (nonliposomal formulation) in Japanese patients with advanced solid tumors at the approved dose level (1.4 mg/m^2; Eisai Inc., data on file; ref. 15), and only a small percentage of free eribulin was observed in plasma

Table 3. TEAEs in the Q3W and Q2W dosing groups (any grade reported in ≥20% of patients in either dosing group).

	E7389-LF Q3W total ($n = 12$)				E7389-LF Q2W total ($n = 9$)			
TEAEs, *n* (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hematologic events								
Anemia	2 (16.7)	2 (16.7)	3 (25.0)	0	1 (11.1)	0	2 (22.2)	0
Thrombocytopenia	2 (16.7)	1 (8.3)	1 (8.3)	1 (8.3)	1 (11.1)	1 (11.1)	1 (11.1)	0
Leukopenia	1 (8.3)	2 (16.7)	5 (41.7)	2 (16.7)	1 (11.1)	3 (33.3)	3 (33.3)	0
Neutropenia[a]	1 (8.3)	1 (8.3)	1 (8.3)	7 (58.3)	0	2 (22.2)	2 (22.2)	4 (44.4)
Lymphopenia	0	3 (25.0)	2 (16.7)	0	0	3 (33.3)	1 (11.1)	0
Nonhematologic events								
Nausea	8 (66.7)	2 (16.7)	0	0	1 (11.1)	1 (11.1)	0	0
Alopecia	6 (50.0)	0	0	0	1 (11.1)	0	0	0
AST increased	4 (33.3)	2 (16.7)	1 (8.3)	0	4 (44.4)	0	1 (11.1)	0
ALT increased	3 (25.0)	1 (8.3)	2 (16.7)	0	2 (22.2)	3 (33.3)	0	0
Decreased appetite	3 (25.0)	1 (8.3)	0	0	2 (22.2)	0	0	0
Rash	3 (25.0)	0	0	0	1 (11.1)	2 (22.2)	0	0
Dysgeusia	3 (25.0)	0	0	0	1 (11.1)	0	0	0
Pyrexia	3 (25.0)	0	0	0	0	0	0	0
Constipation	2 (16.7)	0	0	0	2 (22.2)	0	0	0
Fatigue	2 (16.7)	0	0	0	2 (22.2)	0	0	0
Stomatitis	2 (16.7)	0	0	0	2 (22.2)	0	0	0
Pruritus	2 (16.7)	0	0	0	1 (11.1)	1 (11.1)	0	0
γ-glutamyltransferase increased	1 (8.3)	0	2 (16.7)	0	1 (11.1)	0	1 (11.1)	0
Peripheral sensory neuropathy	1 (8.3)	0	0	0	1 (11.1)	0	1 (11.1)	0
Hypoalbuminemia	0	2 (16.7)	0	0	1 (11.1)	2 (22.2)	0	0
Hypophosphatemia	0	1 (8.3)	2 (16.7)	0	0	1 (11.1)	0	0

Note: Percentages are based on the total number of patients in the safety analysis set within the relevant treatment group. A patient with two or more adverse events in the same preferred term was counted only once for that preferred term. Adverse-event terms were coded using the Medical Dictionary for Regulatory Activities version 23.1. Adverse events were graded using CTCAE version 4.03. Treatment-related TEAEs include TEAEs with missing causality and TEAEs that were considered by the investigator to have a reasonable possibility of relation to the study drug.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; E7389-LF, eribulin liposomal formulation; Q2W, every 2 weeks; Q3W, every 3 weeks; TEAE, treatment-emergent adverse event.

[a]Granulocyte colony-stimulating factor (filgrastim) was given to 7 patients in the Q3W group and 3 patients in the Q2W group for prevention of grade 3 to 4 neutropenia.

(**Fig. 2**). The PK data demonstrated a dose-dependent increase in the means of the C_{max}, the AUC from zero time to time of last quantifiable concentration [$AUC_{(0\text{-}t)}$], and the AUC from zero time extrapolated to infinite time [$AUC_{(0\text{-}inf)}$] of total eribulin (Supplementary Table S2). The mean $AUC_{(0\text{-}t)}$ of free eribulin was less than 1% of the mean $AUC_{(0\text{-}t)}$ of total eribulin at all E7389-LF dose levels. The mean $t_{½}$ of total eribulin at the E7389-LF dose levels of 1.0 mg/m^2, 1.5 mg/m^2, and 2.0 mg/m^2 were 25.4, 27.4, and 23.9 hours, respectively, and dose independent.

Biomarker analyses

Fifty-six of the 81 serum biomarkers (including both endothelial cell/vasculature and immune response–related biomarkers) were analyzed, as less than 20% of samples were below the lower limit of

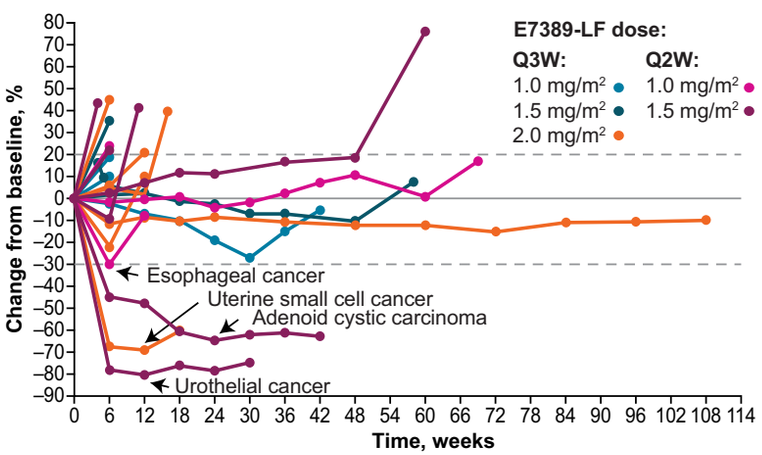

Figure 1.
Percentage change from baseline in sum of tumor diameters over time per RECIST v1.1. E7389-LF, eribulin liposomal formulation; Q2W, every 2 weeks; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria In Solid tumors, version 1.1.

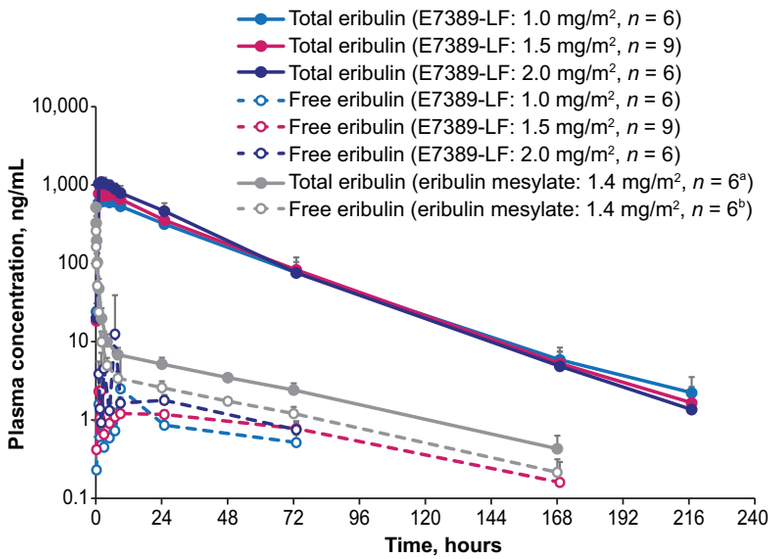

Figure 2.

Plasma concentration profiles of total and free eribulin after administration of E7389-LF (liposomal formulation) or eribulin mesylate (nonliposomal formulation). Total eribulin (E7389-LF), encapsulated and released eribulin in both plasma protein bound and unbound forms; free eribulin (E7389-LF), released from liposomes and plasma protein unbound form; total eribulin (eribulin mesylate), plasma protein bound and unbound eribulin; free eribulin (eribulin mesylate), plasma protein unbound eribulin. Plasma concentrations are shown as mean + SD. Plasma concentrations after administration of E7389-LF were summarized by combining the individual concentration data from both the Q2W and the Q3W dosing groups by dose level and by nominal time point. [a]The total eribulin concentration after administration of eribulin mesylate (nonliposomal formulation) in Japanese patients with advanced solid tumors at the approved dose level (Eisai Inc., data on file; ref. 15). [b]The free eribulin concentration after administration of eribulin mesylate (nonliposomal formulation), which was estimated by multiplying the total eribulin concentration after administration of eribulin mesylate by the plasma protein unbound ratio of 0.5 (roughly assumed by the human plasma protein binding ratio of eribulin: 49% to 65%; ref. 5). E7389-LF, eribulin liposomal formulation; Q2W, every 2 weeks; Q3W, every 3 weeks.

detection at any dose level in the entire cohort (Supplementary Fig. S4). In an integrated analysis using all patients' data in each schedule, changes for these markers were observed in either schedule from baseline to C2D1, C3D1, and C4D1 (Supplementary Table S3). Of note, biomarker levels that increased from baseline in the integrated analysis included endothelial markers [TEK receptor tyrosine kinase (TEK), intercellular adhesion molecule 1 (ICAM1), vascular endothelial growth factor receptor 3 (VEGFR3), and platelet/endothelial cell adhesion molecule 1 (PECAM1)], vasculature marker collagen IV, and immune-related marker interferon gamma (IFNγ). Outside of the integrated analysis, there was an observable trend towards increased endothelial cell and vasculature markers, and IFNγ, from baseline to C2D1 in the Q2W dose group; 1.5 mg/m^2 was generally favored per an observed dose-response trend (**Fig. 3A**). There was also an observed dose-response trend with collagen IV which favored the E7389-LF 1.5 mg/m^2 and 2.0 mg/m^2 dosing of the Q3W dose group (**Fig. 3A**). In the 2.0 mg/m^2 Q3W dose group, endothelial cell and vasculature cell marker levels increased after C2D1 and a large increase in IFNγ was observed from C3D1 to C4D1 (**Fig. 3B**).

Discussion

In this phase I dose-escalation study, E7389-LF was well tolerated in Japanese patients with advanced solid tumors and antitumor effects were demonstrated for several tumor types (**Fig. 1**; Supplementary Fig. S1).

The MTDs were 2.0 mg/m^2 Q3W and 1.5 mg/m^2 Q2W, corresponding to similar planned dose intensities (0.67 mg/m^2/week and 0.75 mg/m^2/week, respectively). Major toxicities were neutropenia, anemia, increased AST, and increased ALT. One DLT (grade 3 febrile neutropenia) was observed at the dose of 2.0 mg/m^2 Q3W; no DLTs occurred with the 1.5 mg/m^2 Q2W regimen. Grade 4 hypophosphatemia (reported as DLT in previous study; ref. 12) was not observed in the Q3W group at doses of 1.0 to 2.0 mg/m^2, and despite the presence of grade 3 events, this dose range was determined to be tolerable. Thus, hypophosphatemia may not substantially affect E7389-LF's tolerability. The neutrophil count nadir occurring between days 8 to 15 may have increased the risk of dose interruption in the Q2W group during administration scheduled on day 15. In the previous study of E7389-LF, treatment-related neutropenia was more often the cause of dose interruption in the Q2W group and two DLTs (grade 3 increased ALT and grade 4 neutropenia) were observed among 3 patients in the Q2W group at doses of 2.0 mg/m^2 (12). Considering the toxicity profiles and the results of the previous study of E7389-LF in Q2W regimen, the recommended dose of E7389-LF for further development in the expansion part was 2.0 mg/m^2 Q3W.

The previous study (12) reported E7389-LF MTDs of 1.4 mg/m^2 Q3W and 1.5 mg/m^2 Q2W, with planned dose intensities of 0.47 mg/m^2/week and 0.75 mg/m^2/week, respectively. Considering the difference in these intensities, the current study offered an opportunity to reevaluate a higher Q3W dose (>1.5 mg/m^2), and establish necessary PK, safety, and tolerability data for E7389-LF in Japanese patients to support further development of this compound globally. The incidence of DLTs and dose levels were similar to the previous E7389-LF study, where 2 patients experienced DLTs (grade 4 hypophosphatemia, $n = 1$; grade 4 increased ALT/AST, $n = 1$) in the Q3W group ($n = 18$) at a dose of 1.5 mg/m^2 and 3 patients experienced

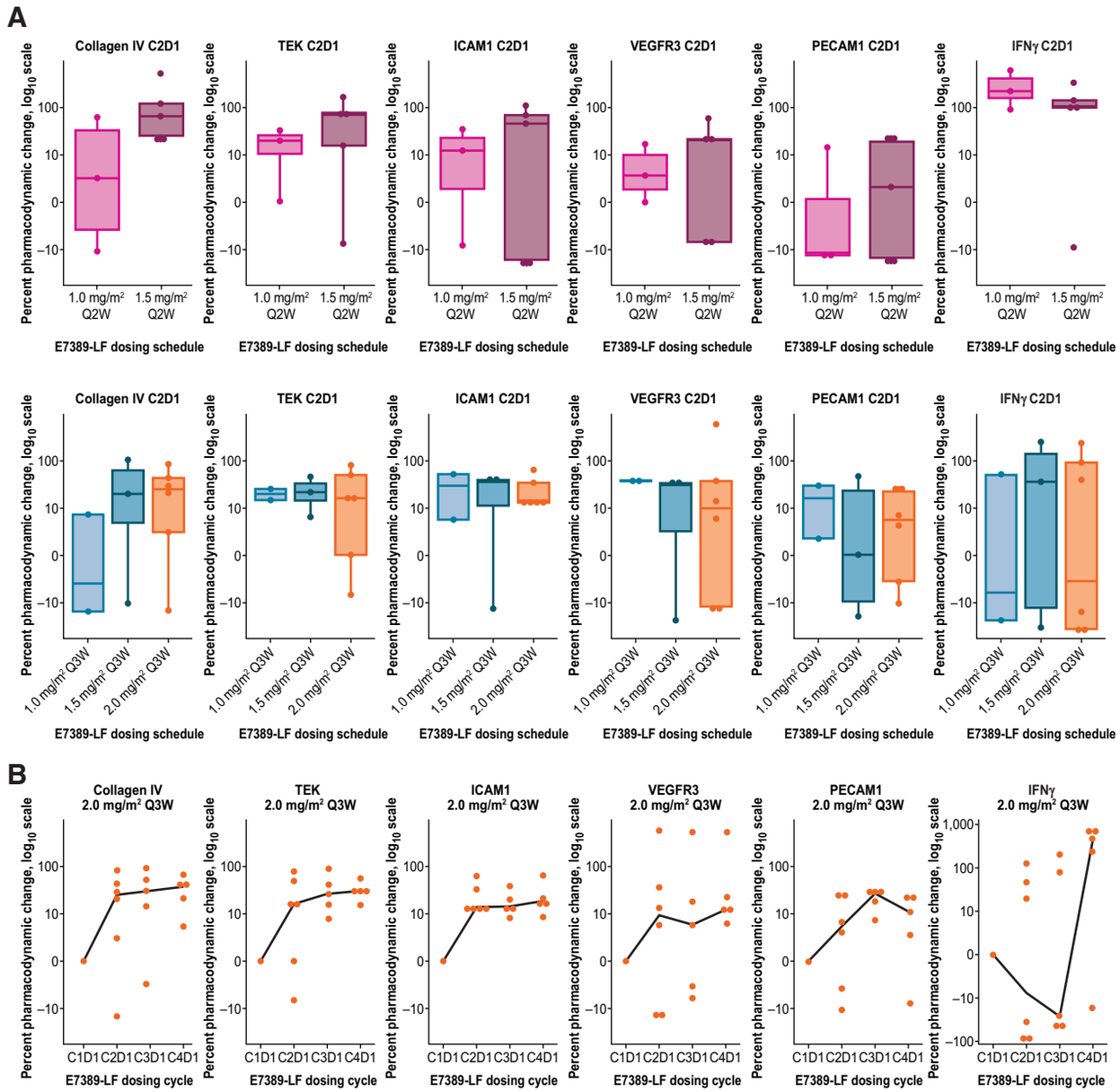

Figure 3.

Biomarker analyses. **A,** Median percent change in select biomarker levels from baseline to C2D1 and **B,** Median percent change in select biomarker levels over time in patients within the E7389-LF Q3W dosing group (2.0 mg/m^2). For box and whisker plots in **A,** the horizontal line represents the median, the box represents the interquartile range, and the whiskers represent the largest or smallest values within 1.5 times the interquartile range (either above the 75th percentile or below the 25th percentile); floating points represent outliers. C#D#, cycle #, day #; E7389-LF, eribulin liposomal formulation; ICAM1, intercellular adhesion molecule 1; IFNγ, interferon gamma; PECAM1, platelet/endothelial cell adhesion molecule 1; Q2W, every 2 weeks; Q3W, every 3 weeks; TEK, TEK receptor tyrosine kinase; VEGFR3, vascular endothelial growth factor receptor 3.

DLTs in the Q2W group ($n = 12$) at 1.5 mg/m^2 (grade 4 febrile neutropenia and grade 3 stomatitis, $n = 1$) and 2.0 mg/m^2 (grade 3 increased ALT, $n = 1$; grade 4 neutropenia, $n = 1$; ref. 12).

The proportion of patients who had a TEAE resulting in dose adjustment was similar to that reported in the previous study of E7389-LF (12). Notably, fewer patients in this study had TEAEs resulting in dose interruption (Q3W/Q2W: 0%/22.2% vs. 25.0%/60.5%), but more patients had TEAEs resulting in dose reduction (Q3W/Q2W: 25.0%/44.4% vs. 5.0%/7.9%; ref. 12). The proportion of patients with TEAEs leading to dose discontinuation was similar between studies; however, TEAEs were different (12). In the previous study, TEAEs leading to discontinuation included abdominal distension, ascites, fatigue, pyrexia, increased bilirubin, decreased appetite, dyspnea, deep vein thrombosis, and vaginal hemorrhage (12). Most of these TEAEs were not associated with discontinuation in this current study; however, the only death that occurred was attributed to

respiratory failure. This variation may be explained by the inclusion of fewer patients in this study, plus the previous study included results from the dose-escalation and dose-expansion phases. In summary, both the Q2W (1.0 mg/m^2, 1.5 mg/m^2) and Q3W E7389-LF dose levels (1.0 mg/m^2, 1.5 mg/m^2, 2.0 mg/m^2) were considered tolerable. As neutropenia was the most common grade ≥3 TEAE and febrile neutropenia was a DLT, additional treatment with filgrastim or prophylactic usage of peg-filgrastim may be beneficial towards patient management and may be considered for inclusion in the recommended dose regimen for further development of this compound, in addition to careful monitoring of blood cell count.

While sample sizes in this analysis were small, E7389-LF demonstrated antitumor activity which warrants further investigation in this population. Moreover, the durable responses in ACC, urothelial cancer, and uterine small cell cancer suggest that liposomes may enhance the efficacy of eribulin.

The much higher plasma concentration of total eribulin compared with free eribulin suggests that most of the eribulin was encapsulated in the liposome after administration of E7389-LF. The plasma concentration of free eribulin after administration of E7389-LF (1.0−2.0 mg/m^2) was generally lower than that after administration of eribulin mesylate (nonliposomal formulation), which is estimated by multiplying the plasma concentration of total eribulin after administration of eribulin mesylate in Japanese patients with advanced solid tumors at the approved dose level (1.4 mg/m^2) by the plasma protein unbound ratio of 0.5 (roughly assumed by the human plasma protein binding ratio of eribulin: 49% to 65%; Eisai Inc., data on file; refs. 5, 15). This suggests that the tumor response of patients receiving E7389-LF was not due to a greater exposure to free eribulin in plasma, but rather due to altered drug delivery into tumors, although the exposure of eribulin to tumor lesions by E7389-LF was not investigated in this clinical study.

While mechanistic advantages of both mesylate-form and liposomal eribulin have been noted as compared with other antimitotic agents (1, 10, 11), an exploratory investigation of eribulin's mechanism of action is imperative in further determining its effect on the immune system. The results of the biomarker analyses suggest that eribulin's mechanism of action may influence the tumor microenvironment via vascular remodeling at both the Q2W and Q3W dose regimens. This is evidenced by the observable trends of increased endothelial cell markers (ie, TEK, ICAM1, VEGFR3, and PECAM1) and vasculature marker collagen IV among the Q2W and Q3W dose groups. In addition, eribulin appears to have an immune-related effect on tumors through increases in IFNγ and its downstream markers C-X-C motif chemokine ligand 11 (CXCL11) and C-X-C motif chemokine ligand 10 (CXCL10; Supplementary Fig. S4). Furthermore, a previous post hoc analysis found that a high baseline absolute lymphocyte count was associated with a longer overall survival with eribulin (but not treatment with physician's choice) in patients with metastatic breast cancer (16). Within this study, both dosing frequencies appear to have exhibited a dose-dependent change in endothelial/vasculature and immune-related biomarkers; however, the limited sample size and analyses completed before database lock may have affected this finding. Furthermore, these biomarkers continued to change after cycle 2, a trend that may be investigated more thoroughly in the dose-expansion part.

In conclusion, the MTDs of E7389-LF were 2.0 mg/m^2 Q3W and 1.5 mg/m^2 Q2W. Further investigation of the 2.0 mg/m^2 Q3W regimen is warranted for specific tumor types; expansion cohorts for breast cancer, ACC, gastric cancer, esophageal cancer, and small cell lung cancer are ongoing at this dose (NCT03207672; refs. 17, 18).

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editing. **N. Yamamoto:** Conceptualization, supervision, investigation, writing–review and editing.

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