Poster No. 980P

Phase 1b Study of a Liposomal Formulation of Eribulin (E7389-LF) + Nivolumab in Patients With Advanced Solid Tumors

Presented at the European Society for Medical Oncology Virtual Congress; September 16–21, 2021

Noboru Yamamoto[1,2], Hanae Ida[1], Toshio Shimizu[1], Yoshiaki Nakamura[3], Makoto Nishino[1], Shu Yazaki[1,4], Yuki Katsuya[1], Jun Sato[1], Takafumi Koyama[1], Satoru Iwasa[1,5], Kazuki Sudo[1,4], Shunsuke Kondo[1,6], Kan Yonemori[1,4], Satoshi Shiono[7], Takuya Suzuki[8], Takao Takase[9], Shuya Takashima[9], Kohei Yamaguchi[10], Taro Semba[11], Kohei Shitara[3]

[1]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan; [2]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; [3]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan; [4]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [5]Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [6]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan; [7]Clinical Operation II, Ono Pharmaceutical Co., Ltd., Osaka, Japan; [8]Japan and Asia Clinical Development Department, Oncology Business Group, Eisai Co., Ltd., Tokyo, Japan; [9]Clinical Data Science Department, Medicine Development Center, Eisai Co., Ltd., Tokyo, Japan; [10]Clinical Pharmacology Science Department, Medicine Development Center, Eisai Co., Ltd., Tokyo, Japan; [11]Oncology Tsukuba Research Department, Oncology Business Group, Eisai Co., Ltd., Tokyo, Japan

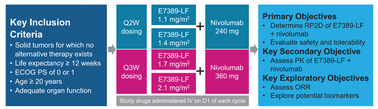
Introduction

- Eribulin is a halichondrin-class microtubule dynamics inhibitor with cytotoxic and vascular remodeling effects leading to tumor immune modulation.[1,2]
- E7389-LF is a liposomal formulation of eribulin designed to enhance antitumor activity and improve the pharmacokinetic profile, with no new or unexpected safety signals compared to eribulin.[3,4]
- Nivolumab is an immunotherapy that blocks programmed death receptor-1.[5]
- The combination of E7389-LF + nivolumab is expected to show antitumor activity by cytotoxic and antitumor immune effects.

Methods

- The primary objectives of this phase 1b study (Study 120) were to determine the recommended phase 2 dose (RP2D) of E7389-LF + nivolumab and evaluate the safety and tolerability of the combination in Japanese patients with advanced solid tumors.
- E7389-LF + nivolumab was administered to 4 cohorts, comprising 2 dosing schedules and 2 doses of study drugs per schedule (**Figure 1**).
  - To assess safety, efficacy, biomarkers, and pharmacokinetic profiles for each dose regimen, at least 6 patients were enrolled in each cohort.

Figure 1. Study design



C#D#, cycle # day #; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; ORR, objective response rate; PK, pharmacokinetics; Q#W, every # week; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; RP2D, recommended phase 2 dose.

- 78 Plasma biomarkers were investigated with AngiogenesisMAP®, Multiplex, and Simoa systems.
  - The concentrations of 27 analytes were below the quantifiable limit; as such, these analytes were omitted from analysis.
- Immune phenotypes were categorized by panCK/CD8 IHC analysis as immune-inflamed (high degree of cytotoxic T cell infiltration), immune-excluded (T cells at invasive margin of tumor, none in tumor bed), and immune-desert (T cells absent from tumor and margins) using tumor biopsy samples from screening and C2D1.[6]

Results

Patients

- At data cutoff, 21 patients (84.0%) were still undergoing treatment. All 4 patients who had discontinued treatment were in the Q2W dosing cohort; 2 had received the E7389-LF 1.1 mg/m² dose and 2 had received the E7389-LF 1.4 mg/m² dose.
- Of the 25 enrolled patients, 16 were male, and the median age was 55 years (range 34–79) (**Table 1**).
  - Most enrolled patients (84.0%) had an Eastern Cooperative Oncology Group performance status of 0.

Dose-Limiting Toxicities

- A dose-limiting toxicity (DLT) was observed in 3 patients, and all DLTs resolved.
  - In the Q3W dosing cohort, 1 patient (who received E7389-LF 1.7 mg/m²) had grade 3 febrile neutropenia.
  - In the Q2W dosing cohort, 1 patient who received E7389-LF 1.1 mg/m² had grade 3 neutropenia (leading to a dose-skip of E7389-LF on day 15); 1 patient who received E7389-LF 1.4 mg/m² had grade 3 febrile neutropenia.

Table 1. Baseline Demographics and Characteristics

Category	E7389-LF Q3W Dose 1.7 mg/m² (n = 6)	E7389-LF Q3W Dose 2.1 mg/m² (n = 6)	E7389-LF Q2W Dose 1.1 mg/m² (n = 7)	E7389-LF Q2W Dose 1.4 mg/m² (n = 6)	Total (N = 25)
Median age (years) (range)	49.0 (42–66)	51.5 (34–79)	61.0 (50–70)	60.0 (44–69)	55.0 (34–79)
Sex, n (%)					
Male	3 (50.0)	4 (66.7)	5 (71.4)	4 (66.7)	16 (64.0)
Female	3 (50.0)	2 (33.3)	2 (28.6)	2 (33.3)	9 (36.0)
Race, n (%)					
Asian (Japanese)	6 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	25 (100.0)
ECOG PS, n (%)					
0	5 (83.3)	5 (83.3)	5 (71.4)	6 (100.0)	21 (84.0)
1	1 (16.7)	0	2 (28.6)	0	3 (12.0)
Missing	0	1 (16.7)	0	0	1 (4.0)
Median bodyweight (kg) (range)	62.15 (43.9–76.6)	65.20 (29.8–109.4)	62.10 (50.4–77.5)	69.75 (57.2–85.7)	63.90 (29.8–109.4)
Primary tumor site, n (%)					
Ovary	2 (33.3)	1 (16.7)	0	1 (16.7)	4 (16.0)
Thymus gland	2 (33.3)	1 (16.7)	0	1 (16.7)	4 (16.0)
Stomach	0	1 (16.7)	2 (28.6)	0	3 (12.0)
Large intestine	1 (16.7)	0	1 (14.3)	0	2 (8.0)
Lung	0	1 (16.7)	1 (14.3)	0	2 (8.0)
Liver	0	0	1 (14.3)	1 (16.7)	2 (8.0)
Other[a]	1 (16.7)	2 (33.3)	2 (28.6)	3 (50.0)	8 (32.0)

[a]Other includes trachea, vulva, uterus, rectum, urinary bladder, parotid, intrahepatic bile duct, and peritoneum (all n = 1).
ECOG PS, Eastern Cooperative Oncology Group performance status; Q#W, every # week.

Safety

- The nadir of neutrophil counts was observed at approximately day 15, and therefore Q3W dosing was preferred.
- The most common grade ≥ 3 severity treatment-related treatment-emergent adverse events overall were neutropenia (52.0%), leukopenia (36.0%), and lymphopenia (16.0%) (**Table 2**).

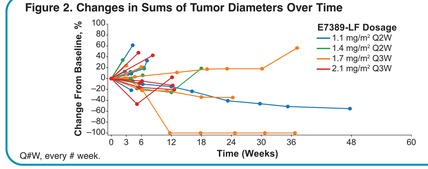
Efficacy

- Overall, a partial response was observed in 4 patients (16.0%) (**Table 3**):
  - 3 Patients in the Q3W dosing cohort (E7389-LF 1.7 mg/m²: 2 patients with thymic carcinoma; E7389-LF 2.1 mg/m²: 1 patient with small cell lung cancer); and 1 patient in the E7389-LF 1.1 mg/m² Q2W dosing cohort with liver cancer.
- Among the 4 patients who had a partial response, all had received prior anticancer therapy.
  - 1 Patient had received carboplatin + paclitaxel, S-1, gemcitabine, an investigational drug in combination with an immune checkpoint inhibitor, and an investigational drug.
  - 1 Patient had received carboplatin + paclitaxel.
  - 1 Patient had received cisplatin + etoposide, atezolizumab + carboplatin + etoposide, amrubicin, and cisplatin + irinotecan.
  - 1 Patient had received cisplatin + gemcitabine, resminostat + S-1, and an investigational drug.
- The overall disease control rate was 48.0% (95% CI: 27.8–68.7) (**Table 3**).
- Changes in the sums of tumor diameters by dose are shown in **Figure 2**.

Pharmacokinetics and Pharmacodynamics

- There were no substantial changes in the overall pharmacokinetic profile of E7389-LF + nivolumab compared to those of each monotherapy.
- Changes were seen in pharmacodynamic markers at cycle (C) 1 day (D) 8 (**Figure 3**).
- Statistically significant changes in all 4 cohorts in any focused pharmacodynamic markers suggested vascular remodeling activity and enhancement of antitumor immunity via interferon gamma (IFNγ) signaling (**Figure 4**).
  - Vasculature-related markers (COL-IV and TIE-2) increased from C1D1 to C2D1.
  - Immune-related markers (IFNγ and IP-10) increased, with a peak at C1D8.
- Among patients who had available samples at screening and at C2D1, 9 patients had an immune-desert or immune-excluded phenotype at screening, and 4 of these patients had an immune-inflamed phenotype at C2D1 (**Table 4**).
  - Changes in immune phenotype were seen at both doses in the Q2W schedule, and at the E7389-LF 1.7 mg/m² dose in the Q3W schedule.

Figure 2. Changes in Sums of Tumor Diameters Over Time



Q#W, every # week.

Table 2. Any-Grade Treatment-Related TEAEs Occurring in ≥ 20% of Patients Overall

MedDRA Preferred Term, n (%)	E7389-LF Q3W Dose 1.7 mg/m² (n = 6) Any Grade	E7389-LF Q3W Dose 1.7 mg/m² (n = 6) Grade ≥ 3	E7389-LF Q3W Dose 2.1 mg/m² (n = 6) Any Grade	E7389-LF Q3W Dose 2.1 mg/m² (n = 6) Grade ≥ 3	E7389-LF Q2W Dose 1.1 mg/m² (n = 7) Any Grade	E7389-LF Q2W Dose 1.1 mg/m² (n = 7) Grade ≥ 3	E7389-LF Q2W Dose 1.4 mg/m² (n = 6) Any Grade	E7389-LF Q2W Dose 1.4 mg/m² (n = 6) Grade ≥ 3	Total (N = 25) Any Grade	Total (N = 25) Grade ≥ 3
Treatment-related TEAEs	6 (100.0)	5 (83.3)	6 (100.0)	4 (66.7)	6 (85.7)	4 (57.1)	6 (100.0)	4 (66.7)	24 (96.0)	17 (68.0)
Leukopenia	4 (66.7)	2 (33.3)	5 (83.3)	3 (50.0)	4 (57.1)	2 (28.6)	4 (66.7)	2 (33.3)	17 (68.0)	9 (36.0)
Neutropenia	5 (83.3)	4 (66.7)	4 (66.7)	3 (50.0)	2 (28.6)	2 (28.6)	5 (83.3)	4 (66.7)	16 (64.0)	13 (52.0)
Anemia	3 (50.0)	0	1 (16.7)	1 (16.7)	2 (28.6)	1 (14.3)	4 (66.7)	0	10 (40.0)	2 (8.0)
Alopecia	1 (16.7)	0	2 (33.3)	0	0	0	6 (100.0)	0	9 (36.0)	0
Stomatitis	2 (33.3)	0	2 (33.3)	0	2 (28.6)	0	3 (50.0)	0	9 (36.0)	0
Lymphopenia	1 (16.7)	0	3 (50.0)	2 (33.3)	1 (14.3)	0	3 (50.0)	2 (33.3)	8 (32.0)	4 (16.0)
Thrombocytopenia	1 (16.7)	0	2 (33.3)	0	1 (14.3)	0	4 (66.7)	0	8 (32.0)	0
ALT increased	2 (33.3)	0	0	0	1 (14.3)	0	4 (66.7)	0	7 (28.0)	0
AST increased	2 (33.3)	0	2 (33.3)	0	1 (14.3)	0	2 (33.3)	0	7 (28.0)	0
Infusion-related reaction	0	0	2 (33.3)	0	2 (28.6)	0	2 (33.3)	0	6 (24.0)	0
Rash	2 (33.3)	0	1 (16.7)	0	2 (28.6)	0	1 (16.7)	0	6 (24.0)	0
Nausea	3 (50.0)	0	1 (16.7)	0	0	0	1 (16.7)	0	5 (20.0)	0
Pyrexia	2 (33.3)	0	1 (16.7)	0	1 (14.3)	0	1 (16.7)	0	5 (20.0)	0

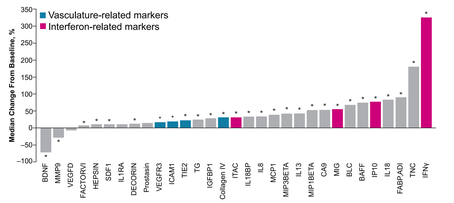
ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; Q#W, every # week; TEAE, treatment-emergent adverse event.

Table 3. Summary of Tumor Responses (per Investigator by RECIST v1.1)

Tumor Response, n (%)	E7389-LF Q3W Dose 1.7 mg/m² (n = 6)	E7389-LF Q3W Dose 2.1 mg/m² (n = 6)	E7389-LF Q2W Dose 1.1 mg/m² (n = 7)	E7389-LF Q2W Dose 1.4 mg/m² (n = 6)	Total (N = 25)
Best overall response					
CR	0	0	0	0	0
PR	2 (33.3)	1 (16.7)	1 (14.3)	0	4 (16.0)
SD	1 (16.7)	3 (50.0)	1 (14.3)	3 (50.0)	8 (32.0)
PD	3 (50.0)	2 (33.3)	4 (57.1)	3 (50.0)	12 (48.0)
Unknown/not evaluable	0	0	1 (14.3)	0	1 (4.0)
Objective response rate (CR + PR) (95% CI)[a]	2 (33.3) (4.3–77.7)	1 (16.7) (0.4–64.1)	1 (14.3) (0.4–57.9)	0 (0–45.9)	4 (16.0) (4.5–36.1)
Disease control rate (CR + PR + SD) (95% CI)[a]	3 (50.0) (11.8–88.2)	4 (66.7) (22.3–95.7)	2 (28.6) (3.7–71.0)	3 (50.0) (11.8–88.2)	12 (48.0) (27.8–68.7)

[a]Calculated with the Clopper-Pearson exact method.
CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; Q#W, every # week; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SD, stable disease.

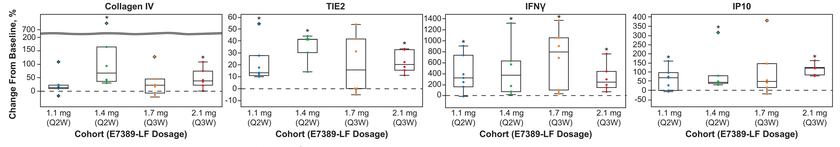
Figure 3. Median Percent Change at Cycle 1 Day 8 in Pharmacodynamic Markers in All E7389-LF + Nivolumab Cohorts



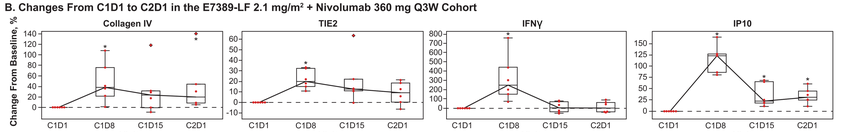
*False-discovery rate-adjusted *P*-value of < 0.05.

Figure 4. Changes in Key Pharmacodynamic Markers With E7389-LF + Nivolumab Treatment

A. Changes at C1D8 in All Dosing Cohorts



B. Changes From C1D1 to C2D1 in the E7389-LF 2.1 mg/m² + Nivolumab 360 mg Q3W Cohort



*Unadjusted *P*-value of < 0.05 (Wilcoxon signed-rank test). ♦ denotes outlier.
C#, cycle; D#, day #; Q#W, every # week.

Table 4. Tumor Biomarkers: Assessment of Immune Phenotypes[a]

E7389-LF Dosage	Primary Tumor Site	Tumor Type	BOR	Immune Phenotype Screening	Immune Phenotype C2D1
1.1 mg/m² Q2W	Vulva	Paget's disease	NE	-	-
	Liver	Intrahepatic cholangiocarcinoma	PR	Desert	Inflamed
	Uterus	Endometrial stromal sarcoma	NE	-	-
	Lung	Small cell lung cancer	SD	Desert	Under test
	Large intestine	Colorectal carcinoma	NE	Desert	-
	Stomach	Gastric cancer	PD	-	-
	Stomach	Mixed adeno-neuroendocrine carcinoma	PD	Desert	-
1.4 mg/m² Q2W	Ovary	Ovarian cancer	PD	Desert	Inflamed
	Rectum	Neuroendocrine tumor	PD	Excluded	Excluded
	Urinary bladder	Urothelial carcinoma	SD	Excluded	Inflamed
	Liver	Pancreatic cancer	PD	Desert	-
	Intrahepatic bile duct	Cholangiocarcinoma	SD	Desert	Excluded
	Thymus gland	Thymic carcinoma	SD	Desert	Desert
1.7 mg/m² Q3W	Parotid	Adenoid cystic carcinoma	SD	Desert	Desert
	Ovary	Endometrioid cancer	PD	Desert	Inflamed
	Large intestine	Colon cancer	PD	Desert	-
	Thymus gland	Thymic carcinoma	PR	Inflamed	Inflamed
	Ovary	Ovarian cancer	PD	Inflamed	-
	Thymus gland	Thymic carcinoma	PR	Inflamed	Under test
2.1 mg/m² Q3W	Lung	Small cell lung cancer	PR	Excluded	Under test
	Trachea	Small cell lung cancer	PD	Under test	Under test
	Ovary	Ovarian cancer	SD	Excluded	-
	Stomach	Gastric cancer	SD	Excluded	Excluded
	Peritoneum	Gastric cancer	PD	Inflamed	Inflamed
	Thymus gland	Thymic carcinoma	SD	Excluded	Under test

Inflamed = high degree of cytotoxic T cell infiltration; excluded = T cells at invasive margin of tumor, none in tumor bed; desert = T cells absent from tumor and margins. Highlighted patients are those who had an immune-desert or immune-excluded phenotype at screening and an immune-inflamed phenotype at C2D1.
[a]As of April 29, 2021.
BOR, best overall response; C2D1, cycle 2 day 1; NE, not evaluable; PD, progressive disease; PR, partial response; Q#W, every # week; SD, stable disease.

Conclusions

- **E7389-LF + nivolumab was tolerable in patients with advanced solid tumors, with antitumor effects.**
- **Based on these results, the RP2D was determined to be E7389-LF 2.1 mg/m² Q3W + nivolumab 360 mg Q3W.**
- **The observed changes in immune phenotype from desert or excluded to inflamed suggest that E7389-LF might enhance immune activity in immune-insufficient types of tumors.**
- **The phase 2 part of this study is ongoing and includes patients with gastric cancer, esophageal cancer, and small cell lung cancer.**

References

1. Smith JA et al. *Biochemistry*. 2010;49:1331-1337.
2. Ito K et al. *Cancer Sci*. 2017;108:2273-2280.
3. Yu Y et al. *Int J Pharm*. 2013;443:9-16.
4. Evans TRJ et al. *Br J Cancer*. 2019;120:379-386.
5. Opdivo (nivolumab). Prescribing information. Bristol Myers Squibb; 2021.
6. Anandappa AJ et al. *Cancer Discov*. 2020;10:185-197.

Conflict of Interest

Dr. Yamamoto: Speaker, consultant, or advisory role for AstraZeneca, Boehringer Ingelheim, Chugai, Cimic, Daiichi-Sankyo, Eisai, Eli Lilly, ONO, Otsuka, Pfizer, Sysmex, Takeda; research funding (inst) from AbbVie, Astellas, Bayer, BMS, Boehringer Ingelheim, Chiome Bioscience, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, GSK, Janssen Pharma, Kyowa-Hakko Kirin, Merck, MSD, Novartis, ONO, Otsuka, Pfizer, Sumitomo Dainippon, Taiho, Takeda.

Acknowledgments

Study sponsored by Eisai Co., Ltd., Tokyo, Japan. Nivolumab provided by Ono Pharmaceutical Co., Ltd., Osaka, Japan. Medical writing support was provided by Heather A. Mitchell, PhD, of Oxford PharmaGenesis Inc., Newtown, PA, USA, and was funded by Eisai Inc., Woodcliff Lake, NJ, USA.

Corresponding author: Noboru Yamamoto, email: nbryamam@ncc.go.jp

ClinicalTrials.gov identifier: NCT04078295