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# A phase II study of halichondrin B analogue eribulin mesylate (E7389) in patients with advanced non-small cell lung cancer previously treated with a taxane: a California Cancer Consortium trial

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## Abstract

**Introduction—**Eribulin mesylate (E7389) is an analog of halichondrin B with a unique mechanism of microtubule binding. The activity and toxicity of eribulin were assessed in patients with advanced non-small cell lung cancer (NSCLC) previously treated with a taxane.

**Methods—**An open-label phase II study included patients with NSCLC previously treated with platinum and taxane-based therapy, with up to two prior cytotoxic regimens, given for metastatic disease or as adjuvant therapy. Patients were stratified by taxane-sensitivity: taxane-sensitive (TS, progression > 90 days after taxane) or taxane-resistant (TR, progression ≤ 90 days after taxane). Patients received an intravenous infusion of eribulin at 1.4 mg/m$^2$ on days 1 and 8 every 21 days. The primary endpoint was objective response rate (ORR) and secondary endpoints included progression-free survival (PFS) and overall survival (OS).

**Results—**Sixty-six patients were accrued. The ORR was 5% with a median duration of response of 7.8 months. In the TS arm, 3 out of 45 patients (7%) achieved a partial response (PR) and another 11 out of 45 (24%) achieved stable disease (SD) for at least 3 months, whereas in the TR arm, no patients achieved a PR and 4 out of 21 (19%) achieved SD for at least 3 months. Median PFS was 2.9 months in the TS subgroup and 1.2 months in the TR subgroup. The median OS was

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12.6 months in the TS subgroup and 8.9 months in the TR subgroup. Toxicities were primarily hematologic; only two patients developed grade 3 neuropathy.

**Conclusions—**Eribulin mesylate is well tolerated and demonstrates activity in pre-treated, taxane-sensitive NSCLC.

### Keywords

Halichondrin B; Eribulin Mesylate; Non-Small Cell Lung Cancer; Taxane-Refractory; Taxane-Sensitive

## Introduction

Lung cancer is the second most common cancer diagnosed in the United States, with 222,520 estimated new cases in 2010.[1] Standard first-line treatment for advanced non-small cell lung cancer (NSCLC) is chemotherapy with a platinum-based doublet. These lead to a predictable response rate of approximately 30% and a median survival of 10–12 months.[2] There is a growing list of FDA approved agents for use in the second and third line, including docetaxel[3], pemetrexed[4] and erlotinib.[5] While these agents have offered modest improvements in survival and quality of life, lung cancer remains the leading cause of cancer-related mortality in both men and women.[1]

Taxanes such as docetaxel selectively bind to polymerized tubulin and promote polymerization, resulting in abnormal microtubule assembly.[6] One clinical advantage of taxanes over other therapies is their activity in tumors lacking functional p53, which is relatively common in NSCLC.[7] While docetaxel has demonstrated efficacy in first-line doublets and as a single agent in subsequent lines of therapy, resistance over time is inevitable. There is a pressing need to explore new agents for patients whose cancer progresses on available therapies.

Eribulin mesylate (E7389) is a tubulin binding agent that inhibits microtubule dynamics via mechanisms distinct from taxanes. This synthetic analog of halichondrin B (a substance isolated from the rare marine sponge *Halichondria okadai*[8]) has shown *in vitro* activity in taxane-resistant cell lines.[9] It was recently approved by the Food and Drug Administration for the treatment of patients with metastatic breast cancer previously treated with anthracycline and taxane therapy and at least 2 prior regimens based on the phase III EMBRACE trial.[10] This trial randomized patients to eribulin mesylate or standard therapy (most often vinorelbine, gemcitabine or capecitabine). Analysis of the 762 patients enrolled demonstrated a response rate of 11% and an improvement in overall survival (OS) from 10.6 months to 13.1 months. A first-in-human phase I study of eribulin mesylate conducted by the California Cancer Consortium established a maximum tolerated dose of 1.4 mg/m$^2$ and two patients with NSCLC achieved a response.[11] In another phase I trial of eribulin mesylate in solid tumors, 1 patient with NSCLC achieved an unconfirmed partial response (PR) and 3 patients with NSCLC achieved stable disease (SD).[12]

This single-arm, open-label phase II study conducted by the California Cancer Consortium sought to determine the safety and efficacy of eribulin mesylate administered as an intravenous infusion at 1.4 mg/m$^2$ on days 1 and 8 of a 21-day cycle in patients with advanced NSCLC previously treated with a taxane or taxane-based therapy and stratified by prior response to taxane-therapy as either taxane-sensitive or -resistant.

## Patients and Methods

### Patient Eligibility

Patients were required to have histologically or cytologically confirmed stage IIIB or IV NSCLC that was recurrent or had progressed after treatment. Patients were required to have been previously treated with platinum-based therapy and a taxane but could have received no more than two prior cytotoxic chemotherapy regimens, given for either metastatic disease or as adjuvant therapy. At least 4 weeks must have elapsed since prior chemotherapy and at least 2 weeks must have elapsed since palliative radiation therapy. Additional key inclusion criteria included at least one measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST v1.0), age ≥ 18 years, Karnofsky performance status ≥ 60% and adequate end-organ function. Patients with grade 2 or greater neuropathy, uncontrolled intercurrent illness or brain metastases that were untreated or still requiring steroids were excluded from this trial.

This trial was reviewed, approved and sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute (ClinicalTrials.gov, identifier NCT00400829) under a contract with the California Cancer Consortium. The local institutional review board at each participating institution approved the protocol. All patients gave written, informed consent.

### Treatment

Eribulin mesylate was administered as a 1–2 minute intravenous infusion at a dose of 1.4 $mg/m^2$ on days 1 and 8 of a 21-day cycle. The dose was reduced to 1.2 $mg/m^2$ for subsequent cycles if any of the following occurred during the previous cycle: grade 3 neutropenia for more than 7 days, febrile neutropenia, grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding or requiring transfusion, or any grade 3 or 4 nonhematologic toxicity that returned to grade 0 or 1 within 14 days. If any of the preceding occurred following the first dose reduction, there was a subsequent dose reduction to 1.0 $mg/m^2$. A maximum of two dose reductions were allowed per patient.

Day 8 treatment was held if the absolute neutrophil count was $< 1.0 \times 10^9/L$ or the platelet count was $< 75 \times 10^9/L$. Doses that were held were deleted and not administered at a later time. If a patient required a dose to be held, the subsequent cycle was reduced by one dose level. Patients requiring more than two dose reductions or a delay in therapy by ≥ 3 weeks were removed from the study.

Premedication to prevent hypersensitivity reactions was not required but prophylactic anti-emetic therapy was given. Colony stimulating factors (CSFs) were not administered during the first course but in the event of febrile neutropenia, use of CSFs was permitted for subsequent courses. Eribulin mesylate treatment continued until unacceptable toxicity, disease progression, investigator decision that discontinuation of therapy was in the best interest of the patient or withdrawal of consent.

### Evaluation of Toxicity and Response

Toxicity was graded according to the common terminology for adverse events (CTCAE) v3.0. CBC with differential and platelet count was performed weekly; serum chemistry panels and physical exams were performed prior to the start of each new course. Baseline tumor assessments were obtained within 4 weeks of start of treatment by computed tomography or magnetic resonance imaging scans of the chest, abdomen and pelvis. Subsequent radiographic evaluation was performed every 6 weeks. Tumor assessments were performed according to RECIST v1.0 criteria and classified as complete response (CR),

partial response (PR), progressive disease (PD) or stable disease (SD). Tumor response of CR or PR was confirmed by a second examination performed at least 4 weeks after the criteria for response were met. Radiographic response was assessed at the annual response review of the California Consortium.

The objective response rate (ORR) was defined as CR + PR / (number of eligible patients); duration of CR or PR was calculated as the time from which measurement criteria were first met for CR or PR until the first date that recurrent or progressive disease was objectively documented. Progression-free survival (PFS) was calculated as the time from the start of treatment to the time of documented progression (per RECIST criteria), symptomatic deterioration or death; patients who were alive and had not yet progressed were censored at their last follow-up. Six patients were taken off-treatment for reasons other than progression and subsequently died of disease; for three of these patients, the date of progression was taken as the date that the patient was taken off treatment due to general deterioration. Two of these patients died within 2 months. The remaining 3 patients were censored at the time they were taken off of treatment. Overall survival (OS) was calculated as the time from the start of treatment to death from any cause or last follow-up.

## Study Design

**Initial Design—**All patients who began treatment with eribulin mesylate were evaluated for toxicity; all eligible patients who began treatment with eribulin mesylate were included in the analysis of efficacy (response rate, PFS and OS). A Simon optimum two-stage design was used in this study, with ORR as the primary efficacy endpoint. Secondary endpoints included OS and toxicity profile. The study design was based on the fact that a true response rate of > 15% would indicate at least some anti-tumor activity and would warrant further study of this regimen, while a true response rate of < 3% would not warrant further study. Using this design, the probability of correctly declaring that a true response rate of 15% warranted further study was 0.90 (power). The probability of declaring that an agent with only a 3% true response rate warranted further study was 0.10 (alpha). In the first stage of accrual, 17 evaluable patients were to be enrolled and assessed. If no response was observed, then accrual would stop, with the conclusion that single agent eribulin mesylate was not promising for further study in these patients. If one or more responses were seen in the first 17 patients, an additional 22 patients would be accrued in the second stage of the study. Three or more responses out of 39 patients would be considered as evidence warranting further study of the regimen, providing other factors such as toxicity and survival also appeared favorable. If only two responses out of 39 patients were observed, further study of eribulin mesylate in these patients would not be warranted.

Patients were stratified based on their response to prior taxane therapy. Patients were considered “taxane-sensitive” (TS) if they achieved a sustained response or SD lasting at least 3 months with taxane based therapy used in the first or second-line setting. All other patients were labeled as “taxane-resistant” (TR). A subgroup analysis was planned to evaluate the outcome of subjects considered taxane-resistant (TR) and taxane-sensitive (TS), separately. If no objective responses were observed among TR patients in the first cohort, then consideration would be given to closing accrual to this subset of patients.

**Amendment to Extend Study—**One objective response was observed in the first 17 patients. For administrative reasons, accrual continued to 41 patients instead of the planned 39. Three of the first 39 patients experienced a PR, suggesting activity of eribulin mesylate. Further review of the three PRs revealed that one patient, initially labeled TR, was more appropriately classified as TS. Thus three of the 20 TS patients experienced a PR while zero of the 21 TR patients experienced an objective response. Given this pattern, the study was

subsequently amended to enroll 25 additional TS patients to confirm the favorable response rate in the TS subgroup while accrual to the TR subgroup was halted.

## Results

### Patient Characteristics

Between 11/21/2006 and 12/04/2009, 66 patients were accrued to this study, all of whom met the key inclusion criteria and began treatment. There were 45 patients in the TS subgroup and 21 in the TR subgroup. Patients received a median of two prior regimens (range 1–2). Eight of the 66 patients (12%) received adjuvant treatment and six of these patients received taxane-based adjuvant therapy. Among the six patients treated with a taxane in the adjuvant setting, four were in the TS subgroup and two were in the TR subgroup. The most common prior regimen was carboplatin and paclitaxel, which was given to 68% of patients (41 out of 66). Table 1 summarizes the baseline demographic and clinical characteristics of these patients, both overall and by taxane sensitivity.

### Study Drug Exposure

All 66 patients were treated with eribulin mesylate 1.4 mg/m$^2$ on days 1 and 8 of a 21-day cycle. A total of 290 cycles of treatment was given to the 66 patients, with a median number of 4 cycles per patient (range: 1–23) as summarized in Table 1. The median number of cycles received was 4 in the TS group (range 1–23) and 2 in the TR group (range 1–8). Only one patient discontinued therapy due to neuropathy (grade 3) and this was after 9 cycles of treatment. Treatment was held or reduced in only 4 other patients for the following reasons: grade 4 neutropenia (one day 8 dose was held, no further interruptions or reductions); grade 3 neutropenia and thrombocytopenia; grade 3 constipation, abdominal pain and hyponatremia; and grade 4 insomnia and fatigue. There were no reports of acute infusional reactions during the administration of eribulin mesylate.

### Efficacy

**Tumor response—**Of the 66 patients, all were included in the assessment of response. Table 2 summarizes the best response achieved. No objective response was noted in the TR group but 29% achieved SD and 19% maintained SD for at least 3 months. In the TS group, three patients achieved PR (7%) and 27 achieved SD (60%) and 22% maintained SD for at least 3 months. There was no association between histologic subtype and response (data not shown). Median PFS was 1.2 months for the TR group and 2.9 months for the TS group. Eighteen of the 21 patients in the TR group and 36 of the 45 in the TS group had died at the time of this report. Median OS was 8.9 months in the TR group (95% CI: 5.0–15.4 months) and 12.6 months in the TS group (95% CI: 9.9–17.5 months). When stratified by taxane sensitivity, there was no significant difference in PFS or OS between patients treated with a taxane in the adjuvant setting and those treated in the metastatic setting.

**Duration of response—**The median duration of response for the three patients that achieved PR was 7.8 months (5.7 months, 7.8 months, and 11.4 months). Eighteen of the 33 patients with SD (55%) had their disease stable for <3 months (median of 1.6 months, range of 0.4 months – 2.9 months) and 15 (45%) had their disease stable for 3 months or longer (median of 5.1 months, range of 3.0 – 11.4 months) since the first disease assessment after treatment start. One patient in the TR group had SD for 9.8 months and 4 patients in the TS group had SD for more than 6 months.

### Treatment Administered and Adverse Effects

The toxicity of eribulin mesylate was manageable, with dose modification primarily due to myelosuppression. Table 3 summarizes the unlikely, possibly, probably or definitely treatment-related adverse events in all 66 patients who received at least one dose of treatment. The most common adverse effects were myelosuppression, constitutional symptoms (most commonly fatigue), metabolic/laboratory abnormalities (most commonly grade 1 elevations in liver function tests and glucose), gastrointestinal toxicities (most commonly grade 1 anorexia and nausea), neurologic toxicities (most commonly grade 1 neuropathy), and pain. The vast majority of these toxicities were grade 1 or 2. The most common grade 3 or 4 adverse effect was myelosuppression, particularly neutropenia (55% of patients), though only one patient had grade 3 febrile neutropenia. Following eribulin mesylate therapy, there were no reported cases of grade 4 neuropathy and only two cases of grade 3 neuropathy (3%), both of which were sensory in nature. There were no cases of grade 3 or 4 cranial or motor neuropathies reported. There were no treatment-related deaths.

## Discussion

This phase II study demonstrates the potential benefit of eribulin mesylate in patients with NSCLC pretreated with a taxane. While the response rate in this patient population was low (5% overall; 7% in the TS group and 0% in the TR group), a sizable number of patients achieved stable disease (33 out of 66, 50% overall; 60% in the TS group and 29% in the TR group). A more telling measure of benefit is maintenance of stable disease for at least 3 months, and while fewer patients met this benchmark (15 out of 66, 23% overall; 24% in the TS group and 19% in the TR group), there was still some indication of activity. This suggests a “clinical benefit rate” (CBR, defined here as CR + PR + SD maintained for at least 3 months) of 27% overall (95% CI: 17% – 40%), higher in the TS group (31%) than in the TR group (19%). It is important to note that this was not a pre-specified endpoint in this trial and should be examined closely in future studies. The clinical benefit of eribulin mesylate was seen in both TS and TR subgroups however, response was only noted in the TS cohort and the benefit of therapy was far greater in these patients. The outcomes of patients treated with a taxane in the adjuvant setting were not significantly different from those who received a taxane in the metastatic setting when stratified by taxane-sensitivity. Future studies limited to or stratified by taxane-sensitivity may have a greater likelihood of demonstrating clinical benefit.

Eribulin mesylate was well tolerated in this trial of pre-treated patients. Neuropathy is a concern, given the similar target of eribulin mesylate and taxanes and the history of taxane therapy in all patients, however only 2 out of 66 patients reported grade 3 sensory neuropathy (3%). The most common adverse effect was myelosuppression, specifically leukopenia and neutropenia however only one patient reported febrile neutropenia.

The activity of eribulin mesylate in patients with breast cancer led to its FDA approval late last year. In the phase II trial of eribulin mesylate in patients with taxane-pretreated, metastatic breast cancer, the reported response rate was 9.3% with a CBR of 17.1%.[13] A similar response rate (9.7%) was noted in a previously reported phase II trial in patients with NSCLC; however, prior taxane therapy was not required in that study.[14] In contrast, the study reported here required prior taxane therapy and stratified patients based on their response to taxane therapy. The results demonstrate a clear difference in activity in patients based on their resistance or sensitivity to taxane therapy. While prior taxane therapy did not preclude activity of eribulin mesylate, prior taxane-resistance did decrease the likelihood of benefit and no patients with TR disease achieved a response to eribulin mesylate.

Our study strongly suggests a benefit of eribulin mesylate in patients with advanced NSCLC previously treated with taxane-therapy, particularly in patients whose disease was initially taxane-sensitive. Adverse effects were manageable with a surprisingly low rate of peripheral neuropathy. In addition, no infusional reactions were noted and pre-medication was not required. While the response rate is modest, a significant number of patients did achieve disease control or SD. Based on its tolerability and the signal of activity, further efforts to define the role of eribulin mesylate in the treatment of advanced NSCLC are warranted and trials in combination with other agents are ongoing.

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**Table 1**

Patient Demographics, Clinical Characteristics and Treatment Delivered

| | Taxane Sensitive | | Taxane Resistant | | Overall | |
|---|---|---|---|---|---|---|
| **Characteristic** | **No. of Patients** | **%** | **No. of Patients** | **%** | **No. of Patients** | **%** |
| Total number of patients | 45 | | 21 | | 66 | |
| Age at Study Entry, years | | | | | | |
| ≤ 60 | 13 | 29 | 13 | 62 | 26 | 39 |
| > 60 | 32 | 71 | 8 | 38 | 40 | 61 |
| Median | 65 | | 55 | | 63 | |
| Range | 42–79 | | 35–83 | | 35–83 | |
| Gender | | | | | | |
| Female | 23 | 51 | 12 | 57 | 35 | 53 |
| Male | 22 | 49 | 9 | 43 | 31 | 47 |
| Histologic Subtype | | | | | | |
| Adenocarcinoma | 28 | 62 | 4 | 19 | 32 | 49 |
| Squamous Cell | 5 | 11 | 5 | 24 | 10 | 15 |
| Other, Non-Small Cell | 12 | 27 | 12 | 57 | 24 | 36 |
| Performance Status | | | | | | |
| Karnofsky 60–80 | 21 | 47 | 8 | 38 | 29 | 44 |
| Karnofsky 80–100 | 24 | 53 | 13 | 62 | 37 | 56 |
| Cycles of Therapy Given | | | | | | |
| 1 | 4 | 9 | 3 | 14 | 7 | 11 |
| 2 | 10 | 22 | 12 | 57 | 22 | 33 |
| 3+ | 31 | 69 | 6 | 29 | 37 | 56 |
| Median | 4 | | 2 | | 4 | |
| Range | 1–23 | | 1–8 | | 1–23 | |

**Table 2**

Best Overall Tumor Response in Eligible Population

| | Taxane Sensitive | | Taxane Resistant | | Overall | |
|---|---|---|---|---|---|---|
| **Best Overall Response** | **No. of Patients** | **%** | **No. of Patients** | **%** | **No. of Patients** | **%** |
| Total number of patients | 45 | | 21 | | 66 | |
| Best Response | | | | | | |
| PR | 3 | 7 | 0 | 0 | 3 | 5 |
| SD | 27 | 60 | 6 | 29 | 33 | 50 |
| PD | 12 | 27 | 13 | 62 | 25 | 38 |
| N/A | 3 | 7 | 2 | 10 | 5 | 8 |
| Overall Survival, months | | | | | | |
| Median (95% CI) | 12.6 (9.9–17.5) | | 8.9 (5.0–15.4) | | 11.6 (8.2–13.7) | |
| Progression Free Survival, months | | | | | | |
| Median (95% CI) | 2.9 (2.5–4.8) | | 1.2 (1.1–2.9) | | 2.7 (1.3–3.9) | |
| Follow-up, months | | | | | | |
| Median (Range) | 39.5 (1.3–41.6) | | 38.1 (0.7–38.1) | | 38.1 (0.7–41.6) | |

**Table 3**

Treatment-Related Adverse Events of Interest or With an Incidence ≥ 10% by CTCAE Grade (n=66) (The toxicities defined as unrelated related to treatment were excluded)

| | Grade 1 or 2 | | Grade 3 or 4 | | All Grades | |
|---|---|---|---|---|---|---|
| **Adverse Event** | **No. of Patients** | **%** | **No. of Patients** | **%** | **No. of Patients** | **%** |
| Hematologic | | | | | | |
| Anemia | 43 | 65 | 0 | 0 | 43 | 65 |
| Leukopenia | 22 | 33 | 19 | 29 | 41 | 62 |
| Neutropenia | 5 | 8 | 36 | 55 | 41 | 62 |
| Thrombocytopenia | 6 | 9 | 1 | 2 | 7 | 11 |
| Constitutional | | | | | | |
| Fatigue | 36 | 55 | 6 | 9 | 42 | 64 |
| Fever, in the absence of neutropenia | 6 | 9 | 1 | 2 | 7 | 11 |
| Dermatologic | | | | | | |
| Alopecia | 13 | 20 | 0 | 0 | 13 | 20 |
| Rash | 7 | 11 | 0 | 0 | 7 | 11 |
| Gastrointestinal | | | | | | |
| Anorexia | 23 | 35 | 0 | 0 | 23 | 35 |
| Constipation | 13 | 20 | 3 | 5 | 16 | 24 |
| Mucositis | 9 | 14 | 0 | 0 | 9 | 14 |
| Nausea | 15 | 23 | 3 | 5 | 18 | 27 |
| Vomiting | 7 | 11 | 2 | 3 | 9 | 14 |
| Lymphatics | | | | | | |
| Edema (limb) | 10 | 15 | 0 | 0 | 10 | 15 |
| Metabolic / Laboratory | | | | | | |
| ALT (SGPT) | 10 | 15 | 0 | 0 | 10 | 15 |
| AST (SGOT) | 14 | 21 | 0 | 0 | 14 | 21 |
| Albumin (low) | 16 | 24 | 1 | 2 | 17 | 26 |
| Alkaline Phosphatase | 11 | 17 | 0 | 0 | 11 | 17 |
| Glucose (high) | 26 | 39 | 1 | 2 | 27 | 41 |
| Potassium (low) | 6 | 9 | 2 | 3 | 8 | 12 |
| Sodium (low) | 9 | 14 | 3 | 5 | 12 | 18 |

| Adverse Event | Grade 1 or 2 | | Grade 3 or 4 | | All Grades | |
|---|---|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % | No. of Patients | % |
| Neurologic | | | | | | |
| Neuropathy, sensory | 18 | 27 | 2 | 3 | 20 | 30 |
| Dizziness | 7 | 11 | 2 | 3 | 9 | 14 |
| Pain | | | | | | |
| Abdominal pain | 6 | 9 | 2 | 3 | 8 | 12 |
| Muscle pain | 9 | 14 | 0 | 0 | 9 | 14 |
| Pulmonary/Upper Respiratory | | | | | | |
| Cough | 9 | 14 | 0 | 0 | 9 | 14 |
| Dyspnea | 7 | 11 | 1 | 2 | 8 | 12 |