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ORIGINAL ARTICLE

A phase 1b, multicenter, open-label, dose-finding study of eribulin in combination with carboplatin in advanced solid tumors and non-small cell lung cancer

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Abstract

Purpose This phase 1b study investigated the maximum tolerated dose (MTD; primary objective), safety, pharmacokinetics, and antitumor activity (secondary objectives) of eribulin combined with carboplatin in patients with solid tumors and, in particular, non-small cell lung cancer (NSCLC).

Methods Two dose-escalation schemes were evaluated with carboplatin, at an area under the curve (AUC) of either 5 or 6 mg/mL·min. Eribulin, dose-escalated from 0.7 to 1.4 mg/m^2 was administered 1 h before (Schedule A) or after (Schedule B) carboplatin as a 2–5-min bolus infusion on days 1 and 8 of a 21-day cycle. Following tolerability assessment, patients with NSCLC were recruited in an expansion cohort.

Results The MTDs were eribulin 1.4 and 1.1 mg/m^2 with carboplatin AUC 5 and AUC 6, respectively. The latter combination was used to treat NSCLC patients in the expansion cohort. Pharmacokinetics of eribulin and carboplatin were generally unaffected by administration sequence (i.e., administration of carboplatin did not significantly affect eribulin C_{max} and AUC_{0-t} and the converse was also observed). In the NSCLC cohort, the objective response rate was 27%. Median overall and progression-free survival durations were 12.1 and 4.2 months, respectively. No unexpected safety findings were observed.

Conclusions The combination of eribulin and carboplatin demonstrated antitumor activity; however, recent therapeutic advances may be more promising approaches for first-line treatment of NSCLC.

Clinical trial registration NCT00268905.

Keywords Phase 1b · Maximum tolerated dose · Eribulin + carboplatin · Advanced solid tumors · NSCLC

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Introduction

Eribulin mesylate ("eribulin") is a fully synthetic analogue of halichondrin B and has a mechanism of action distinct from the vinca alkaloids and taxanes, binding to specific sites on the growing (+) ends of microtubules, inhibiting their growth (polymerization) without affecting depolymerization [1, 2]. Eribulin is currently approved for the treatment of patients with advanced or metastatic breast cancer who were previously treated with an anthracycline and a taxane or patients with unresectable or metastatic liposarcoma who were previously treated with an anthracycline-containing regimen; moreover, eribulin currently remains under investigation for various other malignancies, including non-small cell lung cancer (NSCLC), prostate cancer, and urothelial cancer.

Lung cancer remains the leading cause of cancer deaths in the USA, with a 5-year survival rate of < 20% [3], and NSCLC accounts for > 85% of all lung cancer cases. The standard of treatment for patients with NSCLC continues to change rapidly, with the introduction of targeted agents (e.g., for tumors with *ALK* or *ROS1* rearrangements, or sensitizing *EGFR* mutations), and the development of immune checkpoint inhibitors. However, for the majority of patients with NSCLC, cytotoxic chemotherapy remains the standard of care [4].

Eribulin has shown promising antitumor activity in patients with advanced or refractory NSCLC in phase 1, 2, and 3 studies [5–9]. Specifically, in a randomized phase 3 study (NCT01454934) in patients with advanced NSCLC ($n = 450$), eribulin monotherapy in the third-line or higher setting had a similar median overall survival (OS) and progression-free survival (PFS) to treatment of physician's choice, as well as a manageable safety profile; however, eribulin didn't demonstrate superiority over treatment of physician's choice [9].

While a 2-drug platinum-based combination still represents the recommended standard first-line therapy for the majority of patients with advanced disease, the usual platinum-based combinations for NSCLC appear to have reached a plateau in efficacy, with response rates of 25–35%, time to progression of 4–6 months, median OS of 8–10 months, and 1-year survival rates of 30–40% [4]. Therefore, we felt that the combination of eribulin with a platinum agent, such as carboplatin, could be of interest as a new first-line therapy for advanced disease. We selected carboplatin because it is associated with better tolerability [10] and has generally equivalent efficacy to cisplatin when used in combination with other agents, including taxanes, vinca alkaloid, and gemcitabine [11, 12].

This phase 1b, open-label, dose-finding, multicenter study investigated the maximum tolerated dose (MTD), safety, pharmacokinetics, and antitumor activity of eribulin in combination with carboplatin in patients with advanced solid tumors. The identified MTD was subsequently evaluated in an expansion cohort for patients with NSCLC. Since the sequence of taxanes and platinum agents was previously reported as affecting toxicity and tumor response [13, 14], we also assessed the outcomes following different sequences of eribulin and carboplatin.

Materials and methods

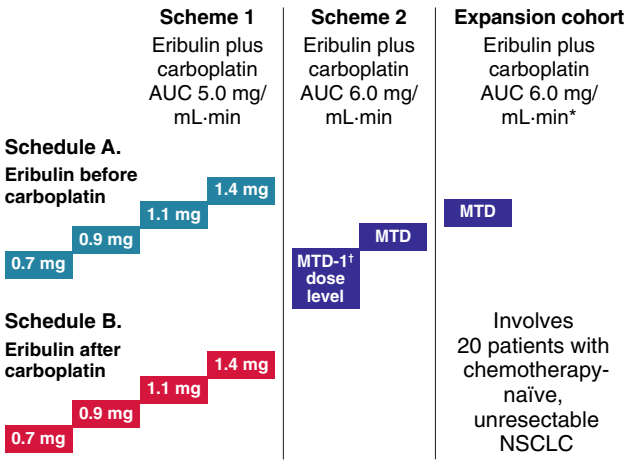
Patient selection

Patients enrolled in this study had to be at least 18 years of age with pathologically confirmed advanced solid tumors that progressed following standard therapy, or for which no standard therapy existed. They were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; life expectancy of at least 3 months; adequate renal, bone marrow, and liver function; and grade 2 or lower chemotherapy or radiation-related toxicities, except alopecia. Specifically, for the expansion cohort, patients were required to have pathologically confirmed advanced NSCLC (Stage IIIB or IV) with measurable disease, not amenable to curative surgical or radiation treatment, and to have received no prior chemotherapy for NSCLC. Informed consent was obtained from all individual participants included in the study. For all patient cohorts, key exclusion criteria included: (1) anticancer therapy (investigational drugs, immunotherapy, gene therapy, hormone therapy, biological therapy, chemotherapy, or radiation) within 3 weeks before study treatment; (2) prior high-dose chemotherapy with hematopoietic stem cell rescue, or stem cell or bone marrow transplant in the past 2 years; (3) pulmonary lymphangitic involvement requiring active treatment; and (4) active symptomatic brain metastases or meningeal carcinomatosis. Other criteria for ineligibility included significant cardiovascular impairment (history of congestive heart failure of greater than grade II severity by New York Heart Association classification, unstable angina or myocardial infarction within the past 6 months, or serious cardiac arrhythmia); preexisting neuropathy of greater than grade 2 severity; prior use of anticoagulants; HIV-positivity; or active hepatitis B or C at study entry. For patients with NSCLC, a prior malignancy (other than carcinoma in situ of the cervix or nonmelanoma skin cancer) was not allowed, unless the prior malignancy was diagnosed and treated at least 5 years previously.

Study design

This was a phase 1b, multicenter, open-label, 2-arm, dose-finding study to determine the MTD of eribulin in combination with carboplatin in patients with advanced solid tumors (NCT00268905). We designed 2 dose-escalation schemes using carboplatin at an area under the plasma concentration–time curve (AUC) of 5 or 6 mg/mL·min (Fig. 1). Intrapatient dose-escalation was not permitted. In Scheme 1 (carboplatin AUC 5.0 mg/mL·min: AUC 5), eribulin was dose escalated from 0.7 to a maximum of 1.4 mg/m^2 in a 3 + 3 design. Patients received eribulin 1 h before (Schedule A) or 1 h after (Schedule B) carboplatin administration. In Scheme 2 (carboplatin AUC 6.0 mg/mL·min: AUC 6), eribulin dose-escalation in a 3 + 3 design began 1 dose level below the MTD from Scheme 1. The preferred treatment schedule (A or B), based on safety and tolerability of Scheme 1, was used in combination with carboplatin AUC 6. If carboplatin AUC 6 + eribulin was tolerated, an additional 20 patients with chemotherapy-naïve stage IIIB or IV NSCLC were to be accrued at the MTD as an expansion cohort. If carboplatin AUC 6 was not tolerated, then an additional 20 patients would be enrolled at the MTD obtained with carboplatin AUC 5 + eribulin. The planned enrollment was approximately 60–85 patients, including 20 patients in the expanded NSCLC cohort.

Eribulin was administered as a 2–5-min bolus infusion on days 1 and 8 of a 21-day cycle. Carboplatin was administered as a 30-min intravenous infusion on day 1 of the 21-day cycle. Patients received study treatment until disease progression, unacceptable toxicity, or withdrawal of consent. This study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by the relevant Institutional Review Boards.



*If carboplatin AUC 6 is not tolerated, then an additional 20 patients will be enrolled at the MTD obtained with carboplatin AUC 5 plus eribulin.

†MTD-1 = 1 level below MTD.

3 Patients are enrolled into each dose level. If none of the 3 patients experience dose-limiting toxicities, 3 patients will be treated at the next dose level. However, if a DLT occurs in 1 of those 3 patients, 3 additional patients (total of 6) will be treated at that dose level.

Fig. 1 Study design

Study objectives

The primary objective was to determine the MTD of eribulin in combination with carboplatin. The secondary objectives were to assess safety, pharmacokinetics, and antitumor activity of the combination in all patients. Separately, the efficacy of eribulin + carboplatin at the MTD in the NSCLC-expansion cohort was also evaluated in terms of objective response rate (ORR), OS, PFS, and duration of response.

Study assessments

The MTD was defined as the highest dose where fewer than 2 out of 6 patients experienced a dose-limiting toxicity (DLT). If the MTDs differed between the 2 schedules, the schedule with the higher MTD was selected for further study. If the MTDs in both schedules were the same, the safety profiles of each schedule would be evaluated to determine the preferred schedule.

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. DLTs were measured in cycle 1 and were defined as nonhematologic or hematologic. Nonhematologic DLT included grade ≥ 3 toxicity (excluding untreated nausea, vomiting, tumor flare, or tumor lyses controllable by aggressive palliative therapy), which resolved to grade 2 or lower toxicity within 14 days. Hematologic DLTs included grade 4 thrombocytopenia, grade 3 thrombocytopenia with clinically significant bleeding, grade 4 neutropenia not reversible to grade 3 or better in ≤ 5 days without growth factor support, febrile neutropenia, or neutropenia associated with bacteremia or sepsis. Anemia or lymphopenia of any grade was not considered a DLT.

Radiologic efficacy assessments per Response Evaluation Criteria In Solid Tumors were performed once every second cycle between day 15 and day 21 in disease areas identified at baseline, and at any other new areas of suspected disease, or sooner if there was evidence of disease progression.

ORR was defined as complete response (CR; complete disappearance of all target lesions) and partial response (PR; at least 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline summed longest diameter). All tumor responses were confirmed ≥ 4 weeks after the date the response was first recorded. OS was measured from the date of first dose of study drug until death from any cause. PFS was measured from the date of first dose of study drug to the date of documented progression of the disease or death from any cause. Duration of response

was measured from the first documented CR or PR until disease progression or death from any cause.

Pharmacokinetic analyses

Pharmacokinetic sampling was performed in all patients during cycle 1 of the dose-escalation phase. Blood and urine samples were collected on days 1, 2, and 3. Plasma and urine levels of eribulin and carboplatin were determined by a validated liquid chromatography–tandem mass spectrometry method on a triple quadrupole mass spectrometer in positive ion mode. Eribulin was extracted from blood and urine samples using liquid–liquid extraction; the sample was then subjected to reverse-phase chromatography. Eribulin and an internal standard were monitored at each analytes' approximate precursor and product ion and quantification was based on a linear 1/x2 weighted regression analysis of the peak area ratios of eribulin and internal standard versus concentrations. Carboplatin was extracted from plasma and urine samples using protein precipitation or solid-phase extraction, respectively. Extracted samples were subjected to strong cation exchange chromatography and carboplatin and internal standards were monitored at each analytes' approximate precursor ion and product ion. Quantification was based on a linear (plasma samples) or quadratic (urine samples) 1/x2 weighted regression analysis of the peak area ratios of carboplatin to internal standard versus concentrations. Pharmacokinetic sampling was not performed for patients in the NSCLC extension arm.

Statistical analyses

The primary and secondary end points were analyzed over 6 cycles following the last patients enrolled or after all patients completed the study, whichever occurred first. The determination of the MTD was based on the first cycle of treatment only.

The safety evaluable population consisted of all patients who received at least a partial dose of the study treatment.

The efficacy-evaluable population comprised chemotherapy-naïve patients with stage IIIB or IV NSCLC not amenable to surgical or radiation treatment and who had completed at least 1 cycle of treatment according to the protocol. We performed no formal statistical treatment comparisons for efficacy. No adjustments for covariates or multiplicity were performed. Efficacy analysis of the NSCLC cohort was purely exploratory and that of the dose determination part of the study was descriptive only. The secondary efficacy analyses of response rates, clinical benefit rate (CBR; defined as the percentage of patients who achieved CR, PR, or stable disease [SD] for ≥ 6 months), and disease control rate (DCR; defined as the percentage of patients who achieved CR, PR, and SD) were calculated with corresponding 2-sided exact 95% confidence intervals (CIs) based on the Clopper–Pearson method; the duration of response, PFS, and OS were summarized using Kaplan–Meier product-limit estimates.

Continuous demographic and other baseline characteristics (e.g., age) were summarized using descriptive statistics. Categorical parameters (e.g., ECOG performance status, sex, or race) were summarized by number and percentage, with missing numbers defined as an additional category.

Pharmacokinetic parameters were calculated using noncompartmental analysis and summarized by scheme, dose, and schedule. No formal statistical analysis was conducted.

Results

The study was conducted between October 25, 2006 and November 22, 2011 at study sites in the USA ($n=4$), Austria ($n=4$), and India ($n=4$). A total of 68 patients were screened, 64 of whom were enrolled and received at least 1 dose of study drug: 43 patients in the dose-finding phase with carboplatin AUC 5, 9 patients in the dose-finding phase with carboplatin AUC 6, and 12 patients with NSCLC in the expansion cohort. Enrollment in the expansion cohort was discontinued due to slow recruitment and changes in the standard of care during the study period; however, data from the 12 patients with NSCLC were used to conduct the study analysis.

Table 1 summarizes patient demographics and baseline disease characteristics. Overall, the median age was 61 (range, 38–80) years; 56% were male, and 52% were white. Some imbalances in demographics and other baseline characteristics between the dose-escalation cohorts and the smaller NSCLC cohort were noted, including race and the proportion of older patients (aged ≥ 65 years). However, the relevance of these differences may be limited because of the relatively small number of patients in the AUC 6 and NSCLC cohorts. The most common tumor types in the dose-escalation portion of the study were gynecological ($n=12$), prostate ($n=12$), colorectal/anal ($n=9$), and lung ($n=8$). Most patients in the dose-escalation cohorts had received at least 1 prior therapy regimen for advanced or metastatic disease. Prior therapy appeared comparable between patients assigned to Schedules A and B (data not shown).

Maximum tolerated dose, dose-limiting toxicities, and preferred schedule

In the carboplatin AUC 5 dose-escalation phase, a DLT (diarrhea) occurred in 1 of 5 patients treated with

Table 1 Patient demographics and disease stage at baseline

Treatment cohort	Eribulin + carboplatin AUC 5 ($n=43$)	Eribulin + carboplatin AUC 6 ($n=9$)	Patients with NSCLC ($n=12$)	Total ($n=64$)
Age				
Median (years)	60.0	59.0	66.5	61.0
Range (years)	38–80	53–75	42–74	38–80
≥ 65 years, n (%)	10 (23.3)	3 (33.3)	9 (75.0)	22 (34.4)
Sex, *n* (%)				
Female	22 (51.2)	5 (55.6)	1 (8.3)	28 (43.8)
Male	21 (48.8)	4 (44.4)	11 (91.7)	36 (56.3)
Race, *n* (%)				
White	23 (53.5)	3 (33.3)	7 (58.3)	33 (51.6)
Black	14 (32.6)	5 (55.6)	0	19 (29.7)
Asian/Pacific Islander	1 (2.3)	0	5 (41.7)	6 (9.4)
Other	5 (11.6)	1 (11.1)	0	6 (9.4)
ECOG PS, *n* (%)				
0	8 (18.6)	0	6 (50.0)	14 (21.9)
1	35 (81.4)	9 (100.0)	6 (50.0)	50 (78.1)
Disease stage				
II	9 (20.9)	0	0	9 (14.1)
III	5 (11.6)	1 (11.1)	4 (33.3)	10 (15.6)
IV	29 (67.4)	5 (55.6)	8 (66.7)	42 (65.6)
Missing/unknown	0	3 (33.3)	0	3 (4.7)
Prior chemotherapy regimens, *n* (%)				
0	0	0	12	12 (18.8)
1	2 (4.7)	0	0	2 (3.1)
2	3 (7.0)	2 (22.2)	0	5 (7.8)
3	12 (27.9)	3 (33.3)	0	15 (23.4)
4	7 (16.3)	1 (11.1)	0	8 (12.5)
5	7 (16.3)	0	0	7 (10.9)
≥ 6	12 (27.9)	3 (33.3)	0	15 (23.4)

AUC area under the curve, *AUC 5* carboplatin AUC 5.0 mg/mL·min, *AUC 6* carboplatin AUC 6.0 mg/mL·min, *ECOG PS* Eastern Cooperative Oncology Group performance status, *NSCLC* non-small cell lung cancer

eribulin 1.4 mg/m^2 on Schedule B. No patient receiving this dose in Schedule A experienced a DLT (Table 2). Thus, we defined the MTD as 1.4 mg/m^2, and the optimum sequence of administration as eribulin followed by carboplatin (Schedule A). This dose and schedule were therefore used for the subsequent dose-escalation and expansion cohorts.

In the carboplatin AUC 6 cohort, DLTs occurred in 1 of 6 patients (febrile neutropenia) at the dose level of 1.1 mg/m^2, and in 2 of 3 patients (febrile neutropenia, neutropenia) at 1.4 mg/m^2 (Table 2). Thus, the MTD of eribulin in combination with carboplatin AUC 6 was 1.1 mg/m^2. This dosing regimen was subsequently used for the NSCLC-expansion cohort.

During the entire study, DLTs were observed in 13 patients during the first cycle, including 4 patients in the NSCLC-expansion cohort.

Pharmacokinetics

Data were collected from 52 patients during cycle 1 and 9 patients during cycle 2. Eribulin and carboplatin plasma profiles appeared to have considerable variation (AUC % coefficient of variation [CV] = 32–89%) within dose and schedule groups. Eribulin maximum serum concentration (C_{max}) and AUC time zero to time "t" ($_{0–t}$) increased in a dose-dependent manner over the 0.7–1.4 mg/m^2 dose range (Fig. 2). The variability in C_{max} and AUC values was high in both schedules, and individual C_{max} and AUC values overlapped among doses (Fig. 2). Administration of carboplatin did not significantly affect eribulin C_{max} and $AUC_{0–t}$, regardless of the administration sequence, nor did eribulin administration affect the pharmacokinetics of carboplatin. Urinary excretion of eribulin was low, with mean values

Table 2 DLTs during cycle 1 in patients treated with eribulin + carboplatin AUC 5 or AUC 6

DLT	Eribulin dose and schedule							
	0.7 mg/m^2		0.9 mg/m^2		1.1 mg/m^2		1.4 mg/m^2	
	A	B	A	B	A	B	A	B
Carboplatin AUC 5, dose-escalation phase	**(*n* = 6)**	**(*n* = 6)**	**(*n* = 6)**	**(*n* = 8)**	**(*n* = 6)**	**(*n* = 3)**	**(*n* = 3)**	**(*n* = 5)**
Patients with DLT	1	1	1	1	1	0	0	1
Grade 4 febrile neutropenia					1			
Grade 4 neutropenia		1[a]						
Grade 4 thrombocytopenia	1							
Grade 3 leukopenia		1[a]						
Grade 3 arthralgia			1[a]					
Grade 3 neuralgia			1[a]					
Grade 3 hyperglycemia				1				
Grade 3 diarrhea								1
Carboplatin AUC 6, dose-escalation phase					**(*n* = 6)**		**(*n* = 3)**	
Patients with DLT					1		2	
Grade 4 febrile neutropenia					1			
Grade 3 febrile neutropenia							1	
Grade 4 neutropenia							1	
Carboplatin AUC 6, NSCLC cohort					**(*n* = 12)**			
Patients with DLT					4			
Febrile neutropenia, grade 3–4					4[b]			
Thrombocytopenia, grade 3–4					3[c]			
Grade 4 leukopenia					1			
Grade 3 gastroenteritis					1			

Schedule A, eribulin then carboplatin; Schedule B, carboplatin then eribulin

AUC area under the curve, *AUC 5* carboplatin AUC 5.0 mg/mL·min, *AUC 6* carboplatin AUC 6.0 mg/mL·min, *DLT* dose-limiting toxicity, *NSCLC* non-small cell lung cancer

[a]1 Patient experienced 2 DLTs

[b]Febrile neutropenia was grade 4 ($n = 2$) or grade 3 ($n = 2$)

[c]Thrombocytopenia was grade 4 ($n = 2$) or grade 3 ($n = 1$)

ranging from 2.5 to 6.1% of the administered dose. In contrast, urinary excretion of carboplatin ranged from 59.8 to 78.9% (data not shown).

Antitumor activity

Eleven of 12 patients with NSCLC completed at least 1 chemotherapy cycle according to the protocol and were evaluable for efficacy (Table 3); 1 patient died due to cardiac failure (not treatment-related). The best response observed was PR in 3 patients resulting in an ORR of 27% (95% CI 6–61%). The CBR and DCR were 27% and 64%, respectively. The median OS was 12.1 months, median PFS was 4.2 months, and the median duration of response was 2.9 months in the NSCLC cohort.

Antitumor activity was also recorded in the dose escalation phases, although no formal efficacy evaluation was conducted. In the carboplatin AUC 5 group, 3 patients achieved CR or PR. The ORR was 9.5% (95% CI 1–30%) when eribulin (at any dose) was given before carboplatin AUC 5, and 4.5% (95% CI 0.1–23%) when eribulin was given after carboplatin AUC 5. In the carboplatin AUC 6 group, no patient achieved a CR and 1 patient achieved a PR. The ORR was 11.1% (95% CI 0.3–48%), regardless of eribulin dose. Examination by tumor type indicated that the maximum number of best overall responses was achieved in patients with prostate cancer, followed by those with lung cancer or ovarian cancer (Online Table S1). Of all patients accrued to this study, 12 were men with castration-resistant prostate cancer (CRPC), all of whom had been treated with docetaxel, and were either refractory to or intolerant of docetaxel. In patients with CRPC, we observed 2 partial responses and 6 patients had a > 49% decline in their prostate-specific antigen levels from baseline (ranging from 49 to 96%). Duration of treatment for patients with CRPC ranged from 6 weeks up to 23 months. However, no definitive conclusions can be drawn, as this study was neither planned nor powered for such analyses.

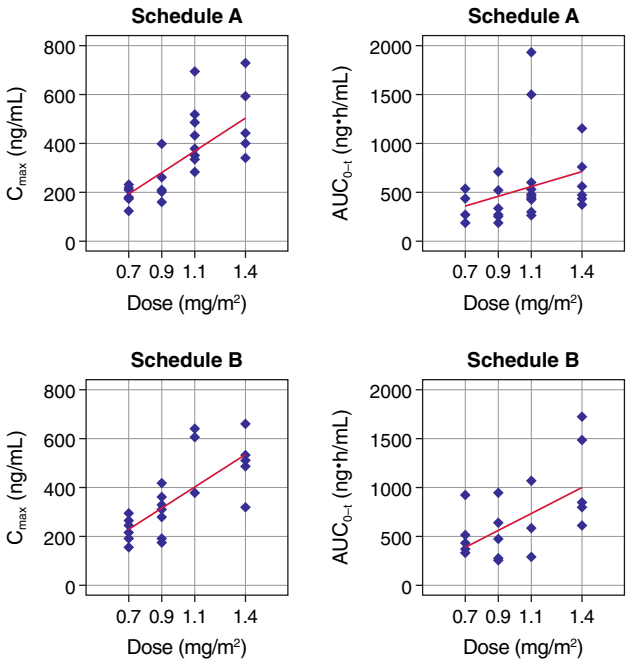


Fig. 2 Eribulin C_{max} and AUC_{0-t} versus dose in Cycle 1 Schedule A: eribulin before carboplatin; Schedule B: eribulin after carboplatin

Safety

Overall, patients received a median number of 3 cycles, with a median of 4 cycles in the NSCLC-expansion cohort. During the dose-escalation phase with AUC 5, patients received a median number of 2 and 4 treatment cycles with Schedules A and B, respectively, and 2.5 treatment cycles with AUC 6. The mean (standard deviation) eribulin relative dose intensity was 81.7% (18.0) for all patients, and 82.7% (20.1) in the NSCLC cohort. In the dose-escalation phase, eribulin relative dose intensity (standard deviation) was 96.1% (6.7) and 72.2% (23.6) with Schedules A and B, respectively, and 86.5% (15.9) with AUC 6. AEs leading to withdrawal of eribulin or carboplatin occurred in 14 (22%) and 13 (20%) patients, respectively; the discrepancy relates to 1 patient who withdrew due to neuralgia specifically with eribulin, rather than carboplatin. The pattern of withdrawal or modification of study treatment due to AEs was nearly identical for eribulin and carboplatin. A summary of AEs leading to dose modification is provided in Table 4.

In general, no unexpected safety findings were observed, and AEs were generally consistent with the safety profile of the individual drugs. Types of AEs were similar across the 3 treatment cohorts, though the severity of AEs differed among cohorts. The most common AEs throughout the study were fatigue (38 of 64 patients; 59%), neutropenia ($n=36$; 56%), thrombocytopenia ($n=26$; 41%), anemia and nausea (both $n=24$; 38%), anorexia ($n=18$; 28%), diarrhea ($n=16$; 25%), and vomiting ($n=15$; 23%). AEs considered potentially related to eribulin and carboplatin occurred in 59 (92%) patients each, with a similar AE profile attributed to both drugs. The most common AEs (in at least 2 patients) of grade 3 or higher severity were neutropenia (27 of 64 patients; 42%), thrombocytopenia ($n=13$; 20%), anemia ($n=9$; 14%), febrile neutropenia ($n=6$; 9%), leukopenia ($n=5$; 8%), hyperglycemia ($n=3$; 5%), and abdominal pain, fatigue, headache, deep vein thrombosis, dyspnea, hypokalemia, and pneumonia (2 patients each; 3%). In the NSCLC cohort, the most common AEs of grade 3 or higher were thrombocytopenia (6 of 12 patients; 50%), neutropenia ($n=5$; 42%), febrile neutropenia ($n=4$; 33%), anemia ($n=3$; 25%), and dyspnea, hypokalemia, leukopenia, and pneumonia (2 patients each; 17%).

Two deaths occurred during the treatment period (on study treatment or within 30 days of the last dose)—1 in the AUC 5 dose-escalation cohort and 1 in the NSCLC cohort. These 2 events, together with 1 death that occurred

Table 3 Response to eribulin + carboplatin in patients with advanced solid tumors and chemotherapy-naïve NSCLC

Response	Eribulin 0.7–1.4 mg/m^2 + carboplatin AUC 5 or 6		
	Solid tumors ($n=52$)	NSCLC ($n=11$)[a]	All patients ($n=63$)
Objective response; *n* (%) [95% CI]	4 (7.7)	3 (27.3) [6.02–60.97]	7 (11.1)
CR	1 (1.9)	0 (0)	1 (1.6)
PR	3 (5.8)	3 (27.3)	6 (9.5)
SD	24 (46.2)	4 (36.4)	28 (44.4)
Clinical benefit rate; n (%)[b] [95% CI]	8 (15.4)	3 (27.3) [6.02–60.97]	11 (17.5)
Disease control rate; n (%)[c] [95% CI]	28 (53.8)	7 (63.6) [30.79–89.07]	35 (55.6)

AUC area under the curve, *AUC 5* carboplatin AUC 5.0 mg/mL·min, *AUC 6* carboplatin AUC 6.0 mg/mL·min, *CI* confidence interval, *CR* complete response, *NSCLC* non-small cell lung cancer, *PR* partial response, *SD* stable diesase

[a]Patients with NSCLC who completed 1 full cycle of treatment were evaluable for response

[b]Clinical benefit rate is defined as objective response (CR + PR) + SD ≥ 6 months

[c]Disease control rate is defined as objective response (CR + PR) + SD

Table 4 Adverse events leading to withdrawal or modification of eribulin or carboplatin ($n=64$)

Adverse event (> 1 patient)	Patients, *n* (%)	Eribulin dose, mg/m^2 (*n*)
Events leading to withdrawal		
Total	14 (21.9)	–
Nervous system disorders	4 (6.3)[a]	**AUC 5**
		0.7 (2)
		0.9 (1)[b]
		AUC 6
		1.1 (1)
Blood/lymphatic disorders	3 (4.7)	**AUC 5**
		0.9 (2)
		AUC 6
		1.1 (1)
Thrombocytopenia	3 (4.7)	**AUC 5**
		0.9 (2)
		AUC 6
		1.1 (1)
Neutropenia	2 (3.1)	**AUC 5**
		0.9 (1)
		AUC 6
		1.1 (1)
Cardiac disorders	2 (3.1)[c]	**AUC 6**
		1.1 (2)
Events leading to dose modification, by affected system/organ/class		
Interruption	2 (3.1)	–
Reduction	15 (23.4)	–
Delay	32 (50.0)	–
Blood/lymphatic system disorders[d]		–
Reduction	14 (21.9)	**AUC 5**
		0.7 (1)
		0.9 (3)
		1.1 (3)
		1.4 (2)
		AUC 6
		1.1 (1)[e]
		Expansion cohort
		1.1 (4)
Delay	25 (39.1)	**AUC 5**
		0.7 (6)
		0.9 (5)
		1.1 (5)
		1.4 (2)
		AUC 6
		1.1 (2)
		1.4 (1)
		Expansion cohort
		1.1 (4)
Events leading to interruption only		
Skin and subcutaneous tissue disorders	2 (3.1)[f]	**AUC 5**
		0.7 (2)[e]

33 days post-treatment, were recorded as serious AEs, but were not considered to be treatment-related by the physicians in charge. The causes of death for these 3 patients were recorded as disease progression, cardiac failure, and disease progression in a patient with an ongoing serious AE of cerebrovascular ischemia, respectively.

Table 4 (continued)

Adverse event (> 1 patient)	Patients, *n* (%)	Eribulin dose, mg/m^2 (*n*)
Events leading to delays only		
Gastrointestinal disorders	4 (6.3)[g]	**AUC 5**
		0.7 (1)
		1.1 (1)
		1.4 (1)
		AUC 6
		1.4 (1)
General disorders and administration site conditions	6 (9.4)[h]	**AUC 5**
		0.9 (1)
		1.1 (1)
		1.4 (3)
		AUC 6
		1.1 (1)
Infections and infestations	3 (4.7)	**AUC 5**
		1.1 (1)
		1.4 (2)
Metabolism and nutrition disorders	3 (4.7)	**AUC 5**
		1.1 (2)
		1.4 (1)
Musculoskeletal and connective tissue disorders	3 (4.7)	**AUC 5**
		0.7 (1)
		0.9 (1)[b]
		1.1 (1)
Nervous system disorders	2 (3.1)	**AUC 5**
		0.7 (1)
		0.9 (1)
Respiratory, thoracic, and mediastinal disorders	2 (3.1)[i]	**AUC 5**
		1.4 (1)
		AUC 6
		1.1 (1)[b]

Adverse events not shown occurred in no more than 1 patient each

AUC 5, carboplatin AUC 5.0 mg/mL·min; AUC 6, carboplatin AUC 6.0 mg/mL·min

[a]1 Patient each with neuralgia, neuropathy, sensorimotor disorder, and syringomyelia

[b]Withdrawal or modification of eribulin dose only

[c]1 Patient each with cardiac failure and coronary artery disease

[d]Predominantly due to neutropenia and thrombocytopenia

[e]Withdrawal or modification of carboplatin dose only

[f]Pruritus in 2 patients

[g]Diarrhea, nausea, and vomiting in 2 patients each

[h]Fatigue and reduced performance status in 2 patients each

[i]Dyspnea in 2 patients

Discussion

This phase 1b study assessed the MTD, safety, pharmacokinetics, and antitumor activity of the combination of eribulin, a microtubule dynamics inhibitor, with carboplatin, a platinum agent, in patients with advanced solid tumors, including an expansion cohort with NSCLC.

The MTD of eribulin was 1.4 mg/m^2 when combined with carboplatin AUC 5 and 1.1 mg/m^2 when given with carboplatin AUC 6. The combination exhibited a manageable safety profile, with neutropenia or febrile neutropenia, the most frequently reported DLTs. Subsequently, an eribulin dose of 1.1 mg/m^2 was used for the NSCLC cohort. The inability to combine carboplatin AUC 6 with the higher eribulin dose of 1.4 mg/m^2 was likely due to overlapping toxicity profiles for the 2 drugs, notably in terms of myelosuppression, as well as the fact that the dose-escalation part of the study enrolled a heavily pretreated patient population.

Eribulin exposure was found to increase in a dose-dependent manner. Urinary excretion was low with eribulin but high with carboplatin, in line with previous findings [15, 16]. Pharmacokinetic analyses showed no significant drug interaction between eribulin and carboplatin. No major differences in C_{max} and AUC_{0-t} (eribulin) or AUC from time zero to infinity ($_{0-\infty}$) (carboplatin) were observed for either eribulin or carboplatin, irrespective of the cohorts, cycles, and schedules, indicating that eribulin administration before or after carboplatin did not affect carboplatin pharmacokinetics and vice versa.

Sporadic cases of clinically relevant tumor responses were observed in the dose-finding cohorts. The prostate-specific antigen response rate observed in this study was comparable to the previously published phase 2 results with eribulin in patients with CRPC [17]. While there have been 2 single-agent eribulin studies performed in CRPC, neither has demonstrated such intense activity in taxane-pretreated patients [17, 18]. There are ample preclinical data on the combination of carboplatin with eribulin in NSCLC models; however, no data exist in prostate cancer models. Carboplatin, along with the other platinates, has been used as a treatment option for patients with CRPC, with limited-to-moderate success [19–23].

Although response rates were calculated, the small patient numbers, the heterogeneous tumor types, and the differing levels of pretreatment preclude any meaningful determination of efficacy in the study population as a whole. In the small NSCLC cohort, the ORR of 27% and the median OS and PFS of 12.1 and 4.2 months, respectively, were within the typical range for platinum-based combination regimens for patients with advanced NSCLC [4].

AEs observed with the eribulin + carboplatin combination were generally consistent with the known safety profiles of each drug, with the exception of neutropenia, albeit the latter was not unexpected. The reported incidence of neutropenia in this study could be attributed to eribulin, which is typically associated with a higher incidence of neutropenia. For example, the incidence of neutropenia associated with eribulin monotherapy was 52% in the pivotal breast cancer study [24] compared to 56% in the current study. The higher incidence of thrombocytopenia in the current study (41% vs. < 10% in the breast cancer study) was expected because thrombocytopenia is commonly associated with carboplatin treatment [10, 24].

Eribulin is also under investigation with various other agents in patients with NSCLC. These include a phase 1 study of eribulin + gemcitabine that identified a recommended phase 2 dose of eribulin 1.0 mg/m^2 and gemcitabine 1000 mg/m^2 on days 1 and 8 every 3 weeks [25]. Eribulin combined with pemetrexed 500 mg/m^2 has also been evaluated in NSCLC, but the combination was tolerated only with a reduction in the eribulin dose to 0.9 mg/m^2 once every 3 weeks and provided no obvious advantage relative to pemetrexed alone in a phase 2 study [26]. In conclusion, although the combination of eribulin and carboplatin demonstrated antitumor activity in this study, other recent advances have suggested more promising approaches for first-line treatment of NSCLC [27–29].

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Compliance with ethical standards

Conflict of interest Sanjay Goel: received funding for the study from Eisai Inc. Kirushna Kumar: received grant for conducting the study from Eisai. Christian Dittrich: received an unrestricted research grant from Eisai. Larisa Reyderman: employee of Eisai Inc. Joseph Aisner: received remuneration for DMC panels from Bristol-Myers Squibb and Merck-Serono. James Song: former employee of Eisai Inc. Daniel P. Petrylak: received consultant fees from AstraZeneca, Bayer, Bellicum, Dendreon, Exelixis, Ferring, Johnson and Johnson, Lilly, Medivation, Millennium, Pfizer, Roche Laboratories, and Sanofi Aventis (Tyme pharmaceuticals discontinued 1/31/17). Received grant support from Agensys, AstraZeneca, Bayer, Clovis, Dendreon, Eli Lilly, Endocyte, Genentech, Innocrin, Johnson and Johnson, Lilly, MedImmune, Medivation, Merck, Millennium, Novartis, Pfizer, Progenics, Roche Laboratories, Sanofi Aventis, and Sotio. Has ownership interest/investment in Bellicum, Tyme. Umang Swami and Minish Jain: no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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