Phase 2 Study Evaluating the Efficacy and Safety of Eribulin Mesylate Administered Biweekly for Patients With Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer

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Introduction

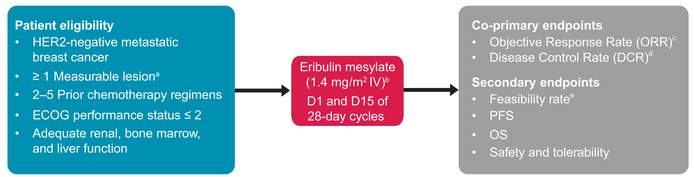
- Eribulin mesylate, a structurally modified synthetic analogue of halichondrin B, is an inhibitor of microtubule dynamics of the halichondrin class of antineoplastic drugs[1]:
  - In preclinical models, eribulin induces vascular remodeling, suppresses cancer-cell migration and invasion, and reverses the epithelial-to-mesenchymal transition associated with a malignant phenotype.[2]
- Neutropenia is one of the most common adverse events (AEs) observed with eribulin treatment.[3–5]
- An analysis across 3 eribulin studies in patients with metastatic breast cancer indicates that grade 3 or 4 neutropenia[3–5]:
  - Occurred in approximately 45% of patients
  - Resulted in dose modification (delay/interruption/reduction) in approximately 25% of patients
  - Most often occurred (86.5%-92.5%) 7 days after eribulin dosing (D8 and D15).
- The approved dosage of eribulin mesylate is 1.4 mg/m^2 administered intravenously (IV) on D1 and D8 of a 21-day cycle.[6]
- A modified biweekly (Q2W) dosing regimen allows 14 days for hematologic recovery between treatment administrations, which may improve the eribulin safety profile.

Methods

Study Design

- This open-label, single-arm, multicenter study (NCT02481050) evaluated the efficacy of eribulin administered biweekly in patients with HER2-negative metastatic breast cancer who have received 2–5 previous chemotherapy regimens (**Figure 1**).
- This study enrolled patients between June 16, 2015 and June 6, 2016 at 12 US oncology sites in the United States.
- Treatment was administered as long as clinical benefit was demonstrated and was discontinued at the occurrence of intercurrent illness, unacceptable toxicity, disease progression, or withdrawal of patient consent.
- Granulocyte colony-stimulating factor (G-CSF) could be administered in accordance with American Society of Clinical Oncology, institutional, or national guidelines; prophylactic G-CSF was not permitted.

Figure 1. Study Design



[a]≥ 10 mm in longest diameter (nonlymph node) or ≥ 15 mm in short-axis diameter (lymph node) by RECIST v1.1.
[b]Equivalent to 1.23 mg/m^2 eribulin (expressed as free base).
[c]ORR = confirmed complete response (CR) + confirmed partial response (PR)
[d]DCR = confirmed CR + confirmed PR + stable disease (SD).
[e]The percentage of patients completing the first 2 and 4 eribulin treatment cycles without a dose delay > 5 days or dose reduction due to an AE.
D, day; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor-2; IV, intravenously; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.

Assessments

- Tumor responses were determined by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1)[7] with imaging studies performed every 8 ± 1 week after the first eribulin dose.
- Safety assessments consisted of the monitoring and recording of all AEs as reported by the investigator, including all Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) grades and serious adverse events (SAEs).

Statistical Methods

- The evaluable analysis set included all patients with evaluable baseline and postbaseline tumor assessments, unless the patient was discontinued due to disease progression or toxicity.
- ORR and DCR were compared with historical data in comparable patient populations[3,4]:
  - A clinically meaningful treatment effect was defined as an ORR > 15% and a DCR of > 60%; corresponding rates deemed of no clinical interest were ≤ 5% and ≤ 45%, respectively.
- PFS and OS were analyzed using Kaplan-Meier product-limit estimates.

Results

- At the time of data cutoff (Dec 31, 2016), 58 patients were enrolled, of whom 57 were evaluable.
  - 53 Patients discontinued treatment (disease progression, n = 45; AE, n = 1; withdrew consent, n = 2; patient choice, n = 4; and other, n = 1).
- Baseline demographics and disease characteristics are summarized in **Table 1**.

Table 1. Demographic, Baseline, and Disease Characteristics

Parameter	Total (N = 58) % (n)[a]
Median (range) age, years	64 (38–85)
Age group	
< 65 years	55 (32)
≥ 65 years	45 (26)
Race	
White	78 (45)
Black or African American	9 (5)
Asian/Indian	5 (3)
American Indian or Alaskan Native	2 (1)
Other/Missing	7 (4)
ECOG performance status	
0	33 (19)
1	60 (35)
2	7 (4)
Hormone-receptor status	
ER+	88 (51)
PR+	76 (44)
Triple negative	12 (7)
Number of prior chemotherapies (metastatic setting)	
1	2 (1)
2	40 (23)
3	28 (16)
4	17 (10)
5	14 (8)
Prior anticancer therapy	
Taxane	86 (50)
Anthracycline	60 (35)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor.
[a]Unless otherwise denoted.

Efficacy

- The ORR was 12% (95% confidence interval: 5–24), and the DCR was 65% (95% CI: 51–77) (**Table 2**).
- Clinical benefit rate was 30% (95% CI: 18–43), and durable SD (≥ 23-week duration from date of first dose) was 18% (95% CI: 9–30).

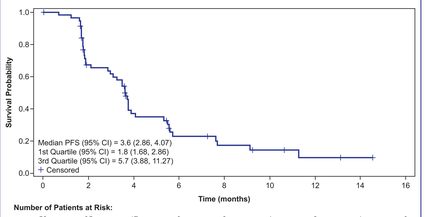
Table 2. Summary of Best Overall Tumor Response

	Total (N = 57) % (n)
ORR[a]	12 (7)
CR	2 (1)
PR	10 (6)
SD	53 (30)
PD	33 (19)
Not evaluable/unknown	2 (1)
DCR[b]	65 (37)
CBR[c]	30 (17)
Durable SD[d]	18 (10)

[a]ORR = confirmed CR + confirmed PR.
[b]DCR = confirmed CR + confirmed PR + SD.
[c]CBR = confirmed CR + confirmed PR + durable SD.
[d]Durable SD = SD with a ≥ 23-week duration.
CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

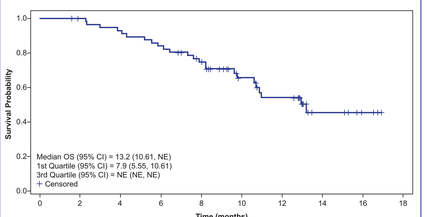
- The feasibility rate was 70% and 50% after cycles 2 and 4, respectively:
  - 50% Of patients received ≥ 1 dose of G-CSF; the median (range) time to G-CSF usage was 4 (0.1–12.4) weeks.
- Median PFS was 3.6 (95% CI: 2.9–4.1) months (**Figure 2**), and median OS was 13.2 (95% CI: 10.6–not estimable) months (**Figure 3**) with 170 days as the median duration of follow-up.

Figure 2. Kaplan-Meier Plot of Progression-free Survival



CI, confidence interval; PFS, progression-free survival.

Figure 3. Kaplan-Meier Plot of Overall Survival



CI, confidence interval; NE, not estimable; OS, overall survival.

Safety

- The median (range) number of eribulin treatment cycles was 3 (1–16), and the median (range) duration of eribulin treatment was 3.1 (0.5–14.7) months.
- During eribulin therapy, 69% of patients experienced dose delay and 28% dose reduction.
- Treatment-emergent AEs (TEAEs) occurring during eribulin therapy are summarized in **Table 3** and **Table 4**:
  - 22% Of patients had grade 1 alopecia and 22% of patients had grade 2 alopecia
  - 72% Of patients had grade 3/4 TEAEs: neutropenia (pooled term), 57%, and peripheral neuropathy (pooled term), 12%. Grade 3 peripheral sensory neuropathy occurred in 9% of patients, with no grade 4 incidence
  - 50% (29/58) Of all patients received at least 1 dose of growth factor (pegfilgrastim n = 21; filgrastim n = 13); 70% (28/40) of patients with neutropenia received growth-factor support.

Table 3. Safety Summary

	Total (N = 58) % (n)
TEAEs	**100 (58)**
Treatment-related TEAEs	**93 (54)**
TEAEs grade ≥ 3	74 (43)
Serious TEAEs[a]	22 (13)
Deaths[b]	3 (2)
Other SAEs	
Life-threatening	2 (1)
Requires inpatient hospitalization or prolongation of existing hospitalization	19 (11)
Persistent or significant disability or incapacity	2 (1)
Important medical events	3 (2)
TEAEs leading to drug withdrawal	2 (1)
TEAEs leading to dose reduction	24 (14)
TEAEs leading to drug interruption	55 (32)

[a]Includes deaths.
[b]Causes of death included sepsis (n = 1) and acute respiratory failure (n = 1); neither were related to treatment.
SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 4. Summary of Most Common TEAEs (Occurring in > 10% of Patients; Safety Population; N = 58)

	All Grades % (n)	Grade 3 % (n)	Grade 4 % (n)
Neutrophil count decreased[a]	**79 (45)**	**28 (16)**	**25 (14)**
Fatigue	48 (28)	2 (1)	0
Alopecia	45 (26)	NA	NA
Constipation	36 (21)	2 (1)	0
Peripheral neuropathy[b]	**29 (17)**	**12 (7)**	**0**
Nausea	26 (15)	0	0
Diarrhea	21 (12)	2 (1)	0
Stomatitis	21 (12)	7 (4)	0
Dyspnea	19 (11)	3 (2)	2 (1)
Decreased appetite	16 (9)	0	0
Cough	14 (8)	0	0
Musculoskeletal pain	14 (8)	0	0
Back pain	12 (7)	0	0
Fall	12 (7)	3 (2)	0
Edema peripheral	12 (7)	0	0
Pyrexia	12 (7)	0	0
Vomiting	12 (7)	2 (1)	0

[a]Data from laboratory results, n = 57.
[b]Pooled term includes neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paresthesia.
A patient with multiple AEs of different grades under a preferred term was counted only once at the highest severity grade.
NA, not applicable; TEAE, treatment-emergent adverse event.

Comparison of Eribulin Clinical Trials With Different Treatment Schedules

Dose schedule	Study 305[3] D1 and D8 of each 21-day cycle	Study 301[4] D1 and D8 of each 21-day cycle	This Study (216) D1 and D15 of each 28-day cycle
Patients, n[a]	503	544	58
Prior chemotherapy regimens, n[b]	2–5	≤ 3	2–5
ORR, % (95% CI)	12 (9.4–15.5)	11 (8.5–13.9)	12 (5–24)
CBR, % (95% CI)	23 (18.9–26.7)	26 (22.6–30.0)	30 (18–43)
PFS, median (95% CI)	3.7 (3.3–3.9) months	4.1 (3.5–4.3) months	3.6 (2.9–4.1) months
OS, median (95% CI)	13.1 (11.8–14.3) months	15.9 (15.2–17.6) months	13.2 (10.7–NE) months
Dose modifications, %			
Delay	49	32[c]	69
Reduction	29	32[c]	28

[a]Patients who received eribulin.
[b]Based on inclusion/exclusion criteria.
[c]Adverse events leading to dose modifications.
CBR, clinical benefit rate; CI, confidence interval; D, day; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Conclusions

- **Objective response rates and survival outcomes of a biweekly eribulin treatment schedule (D1 and D15 of a 28-day cycle) in a pretreated patient population were similar to previously reported phase 3 studies of eribulin.[3,4]**
- **The toxicities associated with biweekly eribulin treatment were manageable.**
- **As a biweekly eribulin schedule could offer easier management of growth factor support for dose intensity, further testing of this treatment schedule is warranted.**

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