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ERIBULIN MESYLATE WITH TRASTUZUMAB AS FIRST-LINE THERAPY FOR LOCALLY RECURRENT OR METASTATIC HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR TWO (HER2)–POSITIVE BREAST CANCER: PRELIMINARY RESULTS FROM A PHASE 2, MULTICENTER, SINGLE-ARM STUDY

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ABSTRACT

Background: Eribulin mesylate, a non-taxane microtubule dynamics inhibitor, was approved in the US for patients with metastatic breast cancer (MBC) who previously received at least 2 chemotherapeutic regimens. This study evaluates the efficacy and safety of eribulin + trastuzumab (T) as first-line therapy for HER2+ MBC.

Methods: Patients with locally advanced (LA)BC or MBC received eribulin mesylate at 1.4 mg/m^2 IV on days 1 and 8 of a 21-day cycle and T at 8 mg/kg, followed by 6 mg/kg on day 1 of subsequent cycles. The objective response rate is the primary endpoint; safety, progression-free survival (PFS), time to response (TTR), and duration of response (DOR) are secondary endpoints. Tumor assessments were evaluated (RECIST 1.1) every 6 weeks for 6 cycles and 6–12 weeks thereafter.

Results: In preliminary results (from 1/19/2012), 26 of 52 planned patients were treated (Table 1). Treatment-emergent adverse events (AEs) are listed in Table 2. Three grade 3 serious AEs were reported (febrile neutropenia, neutropenia, and fatigue). Dose reductions/interruptions occurred in 5 of 26 (19%) patients. Three patients (12%) discontinued from eribulin due to AE (neuropathy: 2 grade 3; 1 grade 2). Individual best patient responses with at least 1 post baseline tumor assessment are 15 PRs, 7 SD, 1 PD, 3 NE. Median TTR was 40 days (95% CI 36, 42). PFS/DOR are immature.

Conclusions: These preliminary results suggest that eribulin + T appears to have considerable activity with acceptable toxicity as first-line therapy for HER2+ LABC/MBC. Further exploration of this combination is warranted.

INTRODUCTION

- Eribulin mesylate is a non-taxane inhibitor of microtubule dynamics of the halichondrin class of antineoplastic drugs[1-3] that has demonstrated a survival benefit relative to commonly used agents in women with metastatic breast cancer (MBC) who previously received at least 2 chemotherapeutic regimens for metastatic disease.[4-7]
  - Eribulin is a structurally modified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*.[1-3]
  - Eribulin has a novel mode of action that is distinct from those of other tubulin-targeting agents; it binds to only the growing + ends, inhibiting the microtubule growth phase without affecting the shortening phase, and causing tubulin sequestration into non-productive aggregates.[1-3,8]
  - In preclinical studies, eribulin induced less neuropathy than did paclitaxel and ixabepilone.[9]
  - The infusion time for eribulin is significantly shorter (2–5 minutes) than most other intravenously administered microtubule-targeting agents. Additionally, eribulin does not require premedications prior to administration.
- Approval of eribulin in the US, EU, Japan, and other countries was based on the Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389 (EMBRACE) study, a phase 3 open-label study, in which women with locally recurrent or MBC were randomly allocated (2:1) to eribulin mesilate or treatment of physician's choice (TPC).[7]
  - Overall survival was significantly improved in women assigned to eribulin (median, 13.1 months; 95% CI 11.8–14.3) compared with TPC (10.6 months; 9.3–12.5; hazard ratio 0.81, 95% CI 0.66–0.99; *P*=.041).[7]
  - The most common adverse events (AEs) in both groups were asthenia or fatigue (270 [54%] of 503 patients on eribulin and 98 [40%] of 247 patients on TPC at all grades) and neutropenia (260 [52%] patients receiving eribulin and 73 [30%] of those on TPC at all grades).[7]
- In view of its antitumor activity in the challenging setting of late-line treatment and its ease of use, assessment of eribulin mesylate in the first-line setting is warranted.
- The focus of this phase 2 trial is to explore the antitumor activity and safety of eribulin mesylate in combination with trastuzumab in first-line therapy for patients with locally recurrent or metastatic HER2+ breast cancer.

OBJECTIVE

To evaluate the efficacy and safety of eribulin + trastuzumab as first-line therapy for patients with locally advanced or metastatic HER2+ breast cancer.

PATIENTS AND METHODS

Eligible Patients

- Female patients ≥18 years of age who have locally recurrent or metastatic HER2+ breast cancer with an Eastern Cooperative Oncology Group (ECOG) status of ≤2 were included in this study. Patients had to have adequate renal, bone, and liver function and a life expectancy of ≥24 weeks.
- Patients were excluded from the study if they had received prior chemotherapy, biologic therapy, or investigational therapy for locally recurrent or metastatic HER2+ breast cancer (patients with prior endocrine therapy or 1 prior treatment with trastuzumab or lapatinib therapy with no additional chemotherapy were permitted).

Dosing and Administration

- Subjects received eribulin mesylate (1.4 mg/m^2 as an intravenous [IV] infusion over 2 to 5 minutes on days 1 and 8 of each 21-day cycle) and trastuzumab as an IV infusion on day 1 of each cycle. Dilution of eribulin in up to 100 mL of 0.9% saline was permitted.
- The initial dose of trastuzumab was 8 mg/kg over a 90-minute period. Subsequent trastuzumab infusions were administered at a dose of 6 mg/kg over a 30-minute period. Trastuzumab was scheduled to be administered immediately after completion of the eribulin mesylate infusion.

Study Assessments

- The primary endpoint of this study was to evaluate objective response rate following first-line combination treatment with eribulin and trastuzumab. The secondary endpoints reported here include assessment of safety and tolerability, time to first response, duration of response, and progression-free survival (PFS).
- Safety was assessed by the monitoring and recording of all AEs, serious AEs, and concomitant medications, and regular monitoring of laboratory values. All AEs were graded per the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0. Serious AEs were collected for 30 days posttreatment and followed until resolution or until the event or sequelae stabilized.

RESULTS

- As of March 5, 2012, 30 of the 52 planned patients have received at least 1 dose of eribulin (safety analysis) and 27 have had 1 post baseline assessment (efficacy analysis).

Table 1. Baseline Demographics and Characteristics

Parameter	Eribulin/trastuzumab (N=30)
Age, years	
Mean (SD)	57.4 (11.4)
Min, max	31, 81
Race, n (%)	
Black or African American	4 (13.3)
White	25 (83.3)
Asian/Pacific	0
American Indian or Alaskan Native	0
Other	1 (3.3)
ECOG status, n (%)	
0	19 (63.3)
1	10 (33.3)
2	1 (3.3)
Metastatic sites, n (%)	
Liver	15 (50.0)
Lung	16 (53.3)
Bone	12 (40.0)
Time from original diagnosis, months	
Mean (SD)	39.5 (44.6)
Min, max	0, 169
ER+ disease, n (%)	21 (70.0)
Prior trastuzumab treatment, n (%)	9 (69.2)
Prior anthracycline treatment, n (%)	7 (23.3)

ER, estrogen receptor; SD, standard deviation.

- The majority of patients were white (83.3%), with a mean (SD) age of 57.4 (11.4) years (**Table 1**).
- Approximately half of patients had liver (50.0%) or lung (53.3%) metastases, and 40.0% of patients had bone metastases.
- Prior treatment with trastuzumab was reported by 30.0% of patients, and prior anthracycline treatment was reported by 23.3% of patients.
- At the time of this interim analysis, the median number of cycles received per patient was 7 (range, 0–17) for eribulin and 8 (range, 1–19) for trastuzumab.

Safety Considerations

Table 2: Treatment-Emergent AEs (All Grades in >10% of Patients, or Grade 3/4/5 in >5% of Patients)

AE preferred term	All grades, n (%) (N=30)	Grade 3/4/5 AEs, n (%) (N=30)
Alopecia	20 (66.7)	0
Neutropenia	17 (56.7)	8 (26.7)
Fatigue	14 (46.7)	0
Peripheral neuropathy	13 (43.3)	4 (13.3)
Dysgeusia	8 (26.7)	0
Nausea	8 (26.7)	0
Anemia	7 (23.3)	0
Decreased appetite	7 (23.3)	0
Diarrhea	6 (20.0)	0
Dyspepsia	6 (20.0)	0
Alanine aminotransferase increased	5 (16.7)	1 (3.3)
Leukopenia	5 (16.7)	0
Pyrexia	5 (16.7)	0
Bone pain	4 (13.3)	0
Constipation	4 (13.3)	0
Dizziness	4 (13.3)	0
Lacrimation increased	4 (13.3)	0
Stomatitis	4 (13.3)	0
Abdominal pain, upper	3 (10.0)	0
Aspartate aminotransferase increased	3 (10.0)	1 (3.3)
Back pain	3 (10.0)	0
Dyspnea	3 (10.0)	0
Musculoskeletal chest pain	3 (10.0)	0
Oral pain	3 (10.0)	0
Sinusitis	3 (10.0)	0
Upper respiratory tract infection	3 (10.0)	0
Febrile neutropenia	2 (6.7)	2 (6.7)

- To date, 3 patients experienced treatment-related serious AEs in the study, including febrile neutropenia, neutropenia, fatigue, bacteremia, and gastroenteritis.
- Dose reductions, interruptions, and discontinuation of therapy due to treatment-emergent AEs occurred in 20.0%, 16.7%, and 13.3% of patients (n=30), respectively.
- Of the 27 patients, 7 are on growth factors.

Efficacy Outcomes

Primary outcome

- In this interim analysis population of 27 patients, the objective response rate was 59.3% (16/27) (**Table 3**).

Table 3: Best Tumor Responses

Response category, n (%)	Eribulin/trastuzumab (N=27)[a]
Objective response rate[b]	16 (59.3)
95% CI	38.8, 77.6
Complete response	1 (3.7)
Partial response	15 (55.6)
Stable disease	7 (25.9)
Progressive disease[c]	1 (3.7)
Not evaluable/unknown	3 (11.1)
Clinical benefit rate[d]	17 (63.0)
95% CI	37.4, 74.5
Disease control rate[e]	23 (85.2)
95% CI	66.3, 95.8

[a]Includes patients with a post-baseline tumor assessment.
[b]Objective response rate includes complete response and partial response.
[c]In this patient the diameter of the target lesion decreased, but a new lesion in the bone was seen and therefore the patient was classified as having progressive disease
[d]Clinical benefit rate includes complete response, partial response, and stable disease (of at least 180 days in duration).
[e]Disease control rate includes complete response, partial response, and stable disease.

- For the 16 patients that had a complete or partial response, the median time to first response was 40 days (range, 36 to 221 days) (**Figure 2**). The duration of the objective response was 240 days (range, 85 to 393* days). The median duration for the 7 patients that reported stable disease was 204 days.
- For all treated patients, the median PFS was 9.2 months (range, 1.35 to 14.19* months) (**Figure 3**).

*Censored time.

Figure 1: Waterfall Graphs of Maximum Percent Change of Tumor Summed Diameters From Baseline for 27 Evaluable Patients

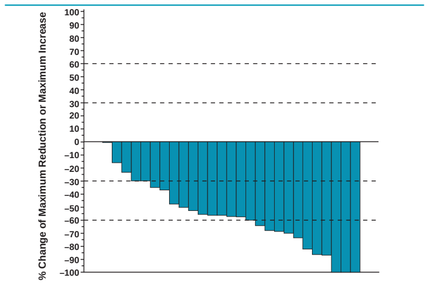


Figure 2: Time to First Response for Patients With Best Overall Response of CR or PR (Based on RECIST version 1.1 criteria) (N=16)

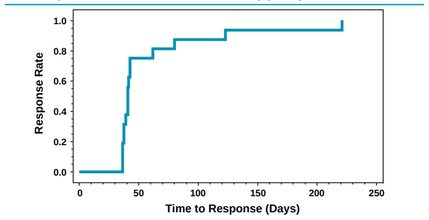
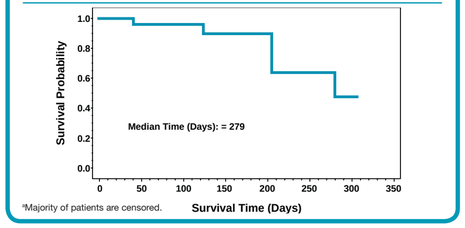


Figure 3: Progression-free Survival



[a]Majority of patients are censored.

DISCUSSION AND CONCLUSIONS

- These preliminary results suggest that the combination of eribulin + trastuzumab appears to have considerable activity with an acceptable toxicity profile as first-line therapy for HER2+ locally advanced or metastatic breast cancer.
  - In this interim analysis population of 27 patients, an objective response rate of 59% was observed.
  - Alopecia, fatigue, neutropenia, and peripheral neuropathy were the most commonly observed treatment-related AEs (all occurred in >30% of patients). The most common grade 3/4 AE was neutropenia, occurring in 8 patients (26.7%).

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