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 dynamic instability agent, was approved in the US for patients with metastatic breast cancer (MBC) who previously received at least 2 chemotherapeutic regimens. This is the first study of eribulin + trastuzumab (T) as first-line therapy for HER2+ MBC.

Methods: Patients with metastatic breast cancer (MBC) or MBC received eribulin mesylate at 1.4 mg/m² IV on day 1 and 8 of a 21-day cycle and trastuzumab at 8 mg/kg IV every 3 weeks by a 90-minute infusion on day 1 of a 3-week cycle. The objective response rate in the primary endpoints, safety, progression-free survival (PFS), time to response, duration of response (DOR) and concomitant medications. Tumor assessments were evaluated by RECIST v1.1 every 9 weeks and CTCAE version 4.0 was used.

Results: 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 (29.4%). All AEs were reported as of 27 patients (51.9%). Tumor responses were estimated for 21 patients (40.4%).

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 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.

RESULTS

1. As of March 5, 2012, 32 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).

Patients received eribulin mesylate (1.4 mg/m² IV) and trastuzumab at 8 mg/kg over a 90-minute period. Subsequent trastuzumab was administered at a dose of 6 mg/kg over a 30-minute period. Eribulin was scheduled to be administered immediately after completion of the eribulin mesylate infusion.

INTRODUCTION

Eribulin mesylate is a non-taxane inhibitor of microtubule dynamics of halichondrin B, a natural product isolated from the marine sponge Halichondria okadae. Eribulin is a novel molecule of action that is distinct from 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. 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 (EMBRACE) 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 mesylate or treatment of physician’s choice (TPC).

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.

Exclusion Criteria

Patients with the following were excluded: active second primary malignancies; other severe or nonremovable concomitant medical conditions; previous malignancy within 5 years (3 years for skin carcinoma in situ or nonmelanoma skin carcinoma) or those that are associated with a high risk of morbidity or mortality; prior use of eribulin, paclitaxel, or trastuzumab; and patients who have not 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/m² 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. Eribulin 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 by the National Cancer Institute’s Common Toxicity 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 sequelate stabilized.

Safety Considerations

Table 3: Best Tumor Responses

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

DISCUSSION AND CONCLUSIONS

These preliminary results suggest that the combination of eribulin+trastuzumab is effective in hormone-responsive and HER2+ locally advanced or metastatic breast cancer. This therapy was well-tolerated with the majority of patients 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 in 93.8% of patients, and prior paclitaxel therapy 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, 1–18) for trastuzumab.

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).