Phase 2, Multicenter, Single-Arm Study of Eribulin Mesylate With Trastuzumab as First-Line Therapy for Locally Recurrent or Metastatic HER2-Positive Breast Cancer☆

Sharon Wilks,[1] Shannon Puhalla,[2] Joyce O'Shaughnessy,[3] Lee Schwartzberg,[4] Erhan Berrak,[5] James Song,[6] David Cox,[5] Linda Vahdat[7]

Abstract

In this multicenter, phase II, single-arm study, 52 patients with recurrent or metastatic HER2-positive (+) breast cancer received first-line eribulin with trastuzumab. The objective response rate (ORR) was 71.2% (n = 37) with a median time to first response (TTR) of 1.3 months; duration of response (DOR) and progression-free survival (PFS) were 11.1 and 11.6 months, respectively. Eribulin/trastuzumab combination resulted in a substantial tumor response with an acceptable safety profile.

Background: The aim of this study was to assess efficacy and safety of eribulin with trastuzumab as first-line therapy for locally recurrent or metastatic HER2+ breast cancer. **Patients and Methods:** In this multicenter, phase II, single-arm study, patients with recurrent or metastatic HER2+ breast cancer received eribulin mesylate at 1.4 mg/m^2 intravenously (I.V.) on days 1 and 8 of each 21-day cycle with an initial trastuzumab dose of 8 mg/kg I.V. on day 1, followed by 6 mg/kg of trastuzumab on day 1 of each subsequent cycle. Tumor assessments were conducted every 6 weeks for the first 6 cycles and every 12 weeks thereafter. The primary end point was ORR, and secondary end points included PFS, TTR, DOR, and safety. **Results:** Fifty-two patients were enrolled. Fifty-one patients (98.1%) had metastatic disease, 25 (48.1%) with liver metastases, 24 (46.2%) with lung metastases, and 19 (36.5%) with bone metastases. Patients received a median of 10.0 cycles of eribulin and 11.0 cycles of trastuzumab. The ORR was 71.2% (n = 37) with median TTR of 1.3 months, DOR of 11.1 months, and PFS of 11.6 months. The most common Grade 3/4 treatment-emergent adverse events were neutropenia in 20 (38.5%) patients, peripheral neuropathy in 14 (26.9%; all Grade 3) patients, fatigue in 4 (7.7%) patients, and febrile neutropenia in 4 (7.7%) patients. **Conclusions:** Because of the high ORR, prolonged median PFS, and acceptable safety profile, combination eribulin/trastuzumab is an acceptable treatment option for locally recurrent or metastatic HER2+ breast cancer.

Clinical Breast Cancer, Vol. 14, No. 6, 405-12 © 2014 The Authors. Published by Elsevier Inc. All rights reserved.
Keywords: Advanced breast cancer, Breast neoplasm, Chemotherapy, Nontaxane microtubule dynamics inhibitor, Oncology

Introduction

In the United States, approximately 5% to 10% of all women have metastatic breast cancer (MBC) at the time of initial diagnosis.[1,2] The prognosis for these patients is poor, with an estimated 5-year survival rate of 24.3%.[1] In a recent survey of 107 published studies involving 39,730 patients, the overall rate of

Presented at the 35th Annual Cancer Therapy & Research Center-American Association for Cancer Research (CTRC-AACR) San Antonio Breast Cancer Symposium, December 4-8, 2012 and the 36th Annual CTRC-AACR San Antonio Breast Cancer Symposium, December 10-14, 2013.

Clinical trial number/registration date: NCT01269346/December 31, 2010

[1]Department of Hematology Oncology, US Oncology-Cancer Care Centers of South Texas, San Antonio, TX
[2]Department of Medicine, Univerisy of Pittsburgh Medical Center, Pittsburgh, PA
[3]Breast Cancer Research, Texas Oncology-Baylor Charles A. Sammons Cancer Center US Oncology, Dallas, TX
[4]Division of Hematology Oncology, West Clinic, Memphis, TN
[5]Medical Affairs, Eisai Inc, Woodcliff Lake, NJ
[6]Biostatistics, Eisai Inc, Woodcliff Lake, NJ
[7]Department of Medicine, Weill Cornell Medical College, New York, NY

Submitted: Jan 31, 2014; Revised: Apr 9, 2014; Accepted: Apr 23, 2014; Epub: Jun 2, 2014

Address for correspondence: Linda Vahdat, MD, Weill Cornell Medical College, 425 East 61st St, 8th Floor, New York, NY 10065
Fax: 212-821-0758; e-mail contact: ltv2001@med.cornell.edu

1526-8209/$ - see frontmatter © 2014 The Authors. Published by Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clbc.2014.04.004

breast cancer with tumors positive for the transmembrane tyrosine kinase receptor was 22.2% (range, 9%-74%).[3] In addition, the frequency of HER2-positivity is increased among patients with metastatic disease.[4]

Trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of HER2,[5] combined with recently approved pertuzumab, is recommended as part of first-line therapy for women with HER2-positive (+) tumors and metastatic disease.[6] Results from multiple clinical trials have demonstrated that the combination of trastuzumab and pertuzumab with any of several conventional chemotherapeutic agents, including carboplatin, docetaxel, vinorelbine, paclitaxel, or capecitabine, is effective for the treatment of HER2-overexpressing metastatic breast cancer (MBC).[7-17]

Eribulin mesylate is a nontaxane inhibitor of microtubule dynamics in the halichondrin class of antineoplastic drugs.[18-21] Specifically, eribulin is a microtubule inhibitor that is a structurally modified synthetic analogue of halichondrin B.[18] Eribulin has a novel mode of action that is distinct from those of other tubulin-targeting agents; it only binds to the growing positive ends, inhibiting the microtubule growth phase without affecting the shortening phase and causing tubulin sequestration into nonproductive aggregates.[18-21] This unique tubulin-based mechanism of action might explain how eribulin is able to overcome taxane resistance and have potentially a wider clinical effect.[22]

Approval of eribulin in the United States, European Union, Japan, and other countries was based on the Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389 (EMBRACE), a phase III open-label study in which women with locally recurrent or metastatic breast cancer were randomly allocated (2:1) to eribulin mesylate or treatment of physician's choice.[23] The phase III EMBRACE study showed significant improvements in overall survival with eribulin versus treating physician's choice of therapy (most often including vinorelbine, gemcitabine, or capecitabine) in previously treated women with MBC. Results from EMBRACE also indicated that the safety and tolerability of eribulin were similar to those for the other chemotherapeutic agents used in the study, and that rates of peripheral neuropathy for eribulin and taxanes were 35% and 45%, respectively. In addition, the authors of the EMBRACE study noted that eribulin has a short infusion time and requires no premedication to prevent hypersensitivity.[23]

Because of its antitumor activity in the challenging setting of late-line treatment, infusion time (1.4 mg/m^2 intravenous [I.V.] over 2-5 minutes on days 1 and 8 of a 21-day cycle), and no premedication requirement to prevent hypersensitivity, assessment of eribulin in the first-line setting for women with MBC is warranted.[23,24] The objective of this phase II trial was to assess the antitumor activity and safety of eribulin in combination with trastuzumab as first-line therapy for patients with locally recurrent or metastatic HER2+ breast cancer.

Patients and Methods

Study Design

In this multicenter, single-arm, phase II trial, we assessed the objective response rate (ORR) of eribulin in combination with trastuzumab in patients with locally recurrent (regardless of resectability) or metastatic HER2+ breast cancer. The study had 3 phases: screening and baseline, six 21-day cycles of eribulin with trastuzumab, and an extension phase in which patients who completed the initial 6 cycles continued to receive study treatment until the development of progressive disease (PD) or until another withdrawal criterion was met.

The study was conducted in accordance with the Declaration of Helsinki (2008), and the protocol and informed consent forms were submitted for approval to institutional review boards by the primary investigators. All patients provided written informed consent before undergoing any study-related procedures.

Patients

Women $\geq$ 18 years of age were eligible for inclusion if they met the following criteria: histologically or cytologically proven recurrent or metastatic adenocarcinoma of the breast with at least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; a HER2+ tumor determined by a score of 3+ on immunohistochemistry staining or gene amplification by fluorescence in situ hybridization; life expectancy of $\geq$ 24 weeks; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; $\geq$ 12 months since previous neoadjuvant or adjuvant chemotherapy (no washout period for previous adjuvant trastuzumab); $\geq$ 2 weeks since previous radiotherapy or endocrine therapy, trastuzumab, or lapatinib, with complete recovery from the effects of these interventions; and adequate renal, bone marrow, liver, and cardiac function. Previous hormonal therapy was allowed.

Patients were excluded if they had received previous chemotherapy, biologic therapy, or investigational therapy for locally recurrent or metastatic HER2+ breast cancer; had previous exposure of $>$ 360 mg/m^2 of doxorubicin or $>$ 720 mg/m^2 of epirubicin; preexisting Grade 3 or 4 neuropathy; or clinically significant cardiovascular impairment (history of congestive heart failure greater than New York Heart Association [NYHA] Class II; unstable/active angina or myocardial infarction $\leq$ 6 months before day 1, or serious cardiac arrhythmia).

Treatment

Patients received 6 cycles of eribulin mesylate 1.4 mg/m^2 administered I.V. with infusion over 2 to 5 minutes on days 1 and 8 of each 21-day cycle and trastuzumab 8 mg/kg I.V. over 90 minutes on day 1 of cycle 1. Thereafter, trastuzumab 6 mg/kg was infused over 30 minutes on day 1 of each subsequent 21-day cycle. Dose reductions for eribulin, but not for trastuzumab, were permitted. Two dose reductions (1.1, 0.7 mg/kg) were allowed before consideration of study treatment discontinuation. Eribulin could be continued as monotherapy if trastuzumab was discontinued, and vice-versa.

Concomitant Medications

Any medication that was considered necessary for the patient's welfare and was not expected to interfere with the evaluation of study treatment could be given at the discretion of the investigator. This included granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and erythropoietin, administered according to American Society of Clinical Oncology guidelines and standard practice; stable bisphosphonate doses; and palliative radiotherapy ($<$ 10% of bone marrow). Other antitumor therapies were not permitted.

End Points

Baseline tumor assessments (computed tomography or magnetic resonance imaging scans) of the chest, abdomen, pelvis, and other areas of known disease were performed within 28 days before the first infusion of study treatment, every 6 weeks during the treatment phase, and every 12 weeks in the extension phase. The primary end point was antitumor activity of eribulin with trastuzumab assessed by determining ORR-based investigator review using RECIST 1.1. The ORR was defined as the proportion of subjects who achieved a complete response (CR) plus those who achieved a partial response (PR). To be assigned a status of PR or CR, changes in tumor measurements must have been confirmed in repeat evaluations carried out $\geq$ 4 weeks after the response criteria were first met. Secondary end points included time to first response (TTR) and duration of response (DOR) for patients whose best overall response was CR or PR and progression-free survival (PFS). Quality of life (QoL) was assessed using the European Organisation for Research and Treatment of Cancer QoL assessment tool (QLQ-C30) and breast module BR23 at screening or baseline, every other cycle during the study, and end-of-treatment visit; results are forthcoming and will be presented in a future analysis.

Safety and Tolerability

Safety parameters included adverse events (AEs) and serious AEs (SAEs); hematology and clinical chemistry; physical examinations; periodic measurement of vital signs and electrocardiograms (ECGs); and evaluation of left ventricular ejection fraction (LVEF) using multigated acquisition scans or echocardiograms and were assessed at baseline, every fourth treatment cycle, and at the end-of-treatment visit. AEs had to occur after and not before dosing of study treatment. All AEs were followed until resolution or for 30 days after the subject's last study visit. However, treatment-emergent peripheral neuropathy and alopecia of any grade were followed until resolution or until another anticancer therapy was started. AEs were graded on a 5-point scale according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical Analysis

All efficacy analyses were based primarily on the full analysis set, which included all patients who received $\geq$ 1 dose of study treatment. Baseline demographic and clinical characteristics were summarized. The ORR was determined along with corresponding 2-sided, exact binomial 95% confidence intervals (CIs). TTR, DOR, and PFS were analyzed using Kaplan-Meier product-limit estimates. Disease control rate (DCR; CR + PR + stable disease), clinical benefit rate (CBR; CR + PR + stable disease $\geq$ 6 months), and 95% CIs were also determined. For PFS subgroup analysis, 95% CIs were calculated; because of the small sample size, no covariate adjustment was made in the analysis.

Results

Patient Characteristics

A total of 52 patients (median age of 59.5 years), 51 (98.1%) with metastatic disease, entered the study; 45 patients completed the treatment phase (the first 6 cycles of treatment) and 9 discontinued because of AEs (n = 3), PD (n = 3), or other reasons (n = 3; Table 1). Eight patients were still in the extension phase of the treatment at the time of clinical data cut. Median daily intensity was 0.13 mg/m^2/d (minimum, 0.1; maximum, 1.4) per patient. Mean number of eribulin doses was 23.8 and the median number of cycles received per patient was 10.0 (range, 0-38) for eribulin and 11.0 (range, 1-37) for trastuzumab. No patient received palliative radiotherapy during the study.

Table 1 Demographic and Clinical Characteristics of Study Patients

Category	Eribulin/Trastuzumab (n = 52)
Median Age, Years (Range)	59.5 (31-81)
Race, n (%)	
White	40 (76.9)
Black or African American	11 (21.2)
Asian	1 (1.9)
Ethnicity, n (%)	
Hispanic or Latino	5 (9.6)
Not Hispanic or Latino	47 (90.4)
ECOG Performance Status, n (%)	
0	37 (71.2)
1	14 (26.9)
2	1 (1.9)
Mean Time From Original Diagnosis of Breast Cancer, Years (SD)	3.0 (3.3)
Mean Age at Diagnosis, Years (SD)	56.3 (11.6)
Breast Cancer Stage, n (%)	
IIB	0
IIIA	51 (98.1)
IIIB	0
IV	0
NA	1 (1.9)
Metastatic Breast Cancer, n (%)[a]	51 (98.1)
Metastases, n (%)	
Liver	25 (48.1)
Lung	24 (46.2)
Brain	1 (1.9)
Bone	19 (36.5)
Skin	3 (5.8)
Other	33 (63.5)
Organs Involved, n (%)	
1	15 (28.8)
2	24 (46.2)
$\geq$3	13 (25.0)
Previous Anticancer Therapy, n (%)	
Taxane or anthracycline	25 (48.1)
Trastuzumab or lapatinib	22 (42.3)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.
[a]Fifty-one of 52 patients had metastatic disease at baseline.

Efficacy

Overall, 52 patients in the full analysis set were evaluable for ORR (Table 2). The ORR was 71.2% (n = 37; 95% CI,

Table 2 Tumor Responses

Response Category, n (%)	Eribulin/Trastuzumab (n = 52)
Objective Response Rate; 95% CI	37 (71.2); 56.9-82.9
Complete Response	3 (5.8)
Partial Response	34 (65.4)
Stable Disease	13 (25.0)
Progressive Disease	1 (1.9)
Not Evaluable	1 (1.9)
Clinical Benefit Rate; 95% CI[a]	44 (84.6); 71.9-93.1
Disease Control Rate; 95% CI[b]	50 (96.2); 86.8-99.5

[a]Clinical benefit rate = CR + PR + stable disease (≥ 6 months).
[b]Disease control rate = CR + PR + stable disease.

56.9-82.9), the DCR was 96.2% (n = 50; 95% CI, 86.8-99.5), and the CBR was 84.6% (n = 44; 95% CI, 71.9-93.1). Investigator assessments indicated CR in 3 (5.8%) patients and PR in 34 (65.4%) patients. The median TTR for patients with CR or PR was 1.3 months (95% CI, 1.2-1.4). The median DOR was 11.1 months (95% CI, 6.7-17.8). A summary of percent changes in the total sum of target lesion diameters is shown in Figure 1. The median percent change from baseline was −62.4%. In patients who received a dose reduction (n = 21), tumor response rates were greater compared with those who did not (n = 31) in ORR (17 [81.0%] vs. 20 [64.5%]), DCR (21 [100.0%] vs. 29 [93.5%]), CBR (20 [95.2%] vs. 24 [77.4%]), and durable stable disease (3 [14.3%] vs. 4 [12.9%]).

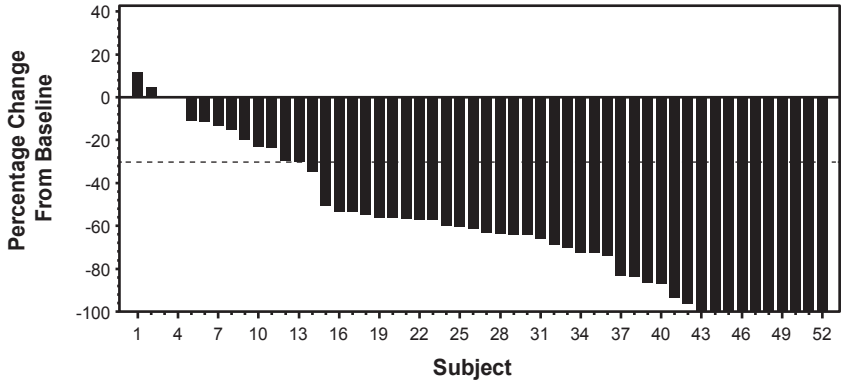
The median PFS was 11.6 months (95% CI, 9.1-13.9; Figure 2) and Kaplan-Meier estimates for the 3-, 6-, 9-, and 12-month PFS rates were 96%, 82%, 67%, and 49%, respectively. Forest plot of PFS subgroup analyses are included in Figure 3. Factors associated with a shorter PFS (> 2-month reduction in PFS vs. the overall median value) were patients with hormone-negative disease (9.5 months; n = 15); estrogen receptor-positive/progesterone receptor-positive (9.2 months; n = 21); baseline ECOG status 1 or 2 (9.2 months; n = 15); < 2 years from adjuvant or neoadjuvant therapy to start of current treatment (5.0 months; n = 6); MBC diagnosed within 3 months of original diagnosis (9.5 months; n = 20); liver involvement (9.5 months; n = 25); and metastases involving 2 organs (9.2 months; n = 24). PFS was extended by > 2 months versus the overall median value in metastases involving the number of target lesions (> 3) (13.9 months; n = 6); however, these subgroups are small, and therefore results should be interpreted with caution.

Safety

All patients reported treatment-emergent AEs (TEAEs), and all reported TEAEs that were considered to be related to either eribulin or trastuzumab (Table 3). Grade ≥ 3 TEAEs according to the Common Terminology Criteria for Adverse Events (CTCAE) were reported by 37 (71.2%) patients and SAEs were reported by 15 (28.8%) of patients.

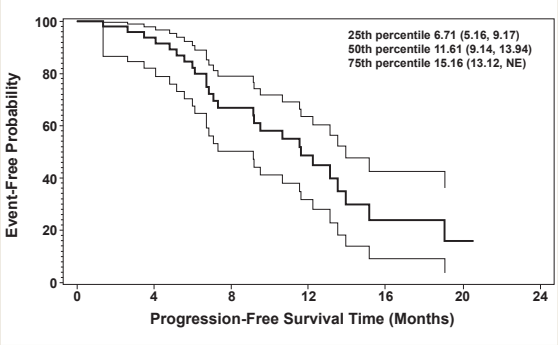
The most common TEAEs (all grades occurring in ≥ 50% of patients) were alopecia (88.5%; n = 46), fatigue (69.2%; n = 36), neutropenia (59.6%; n = 31), and peripheral neuropathy (69.2%; n = 36; as classified from the Standardized Medical Dictionary for Regulatory Activities Queries [SMQ], which includes all forms of neuropathy combined). The most common Grade 3/4 TEAEs (occurring in ≥ 5% of patients) were neutropenia (38.5%; n = 20), peripheral neuropathy (26.9%; n = 14 [SMQ]), fatigue (7.7%; n = 4), febrile neutropenia (7.7%; n = 4), leukopenia (5.8%; n = 3), vomiting (5.8%; n = 3), and hyperglycemia (5.8%; n = 3). Of these, Grade 4 TEAEs were seen for neutropenia and febrile neutropenia. The median time to onset for all peripheral neuropathy was 113 days (95% CI, 69.0-155.0; n = 36) after the initiation of treatment; for Grade 3/4 peripheral neuropathy, median time to onset was 568 days (95% CI, 400.0-not estimable; n = 14). The median duration was 155 days (95% CI, 78.0-351.0; n = 36) for peripheral neuropathy and 23 days (95% CI, 8.0-56.0; n = 14) for Grade 3/4 peripheral neuropathy resolving to Grade 1/2.

Figure 1 Waterfall Graph of Percentage Change in Total Sum of Target Lesion Diameters From Baseline to Post-Baseline Nadir (RECIST 1.1)



Abbreviation: RECIST = Response Evaluation Criteria in Solid Tumors.

Figure 2 Kaplan-Meier Plot of Progression-Free Survival

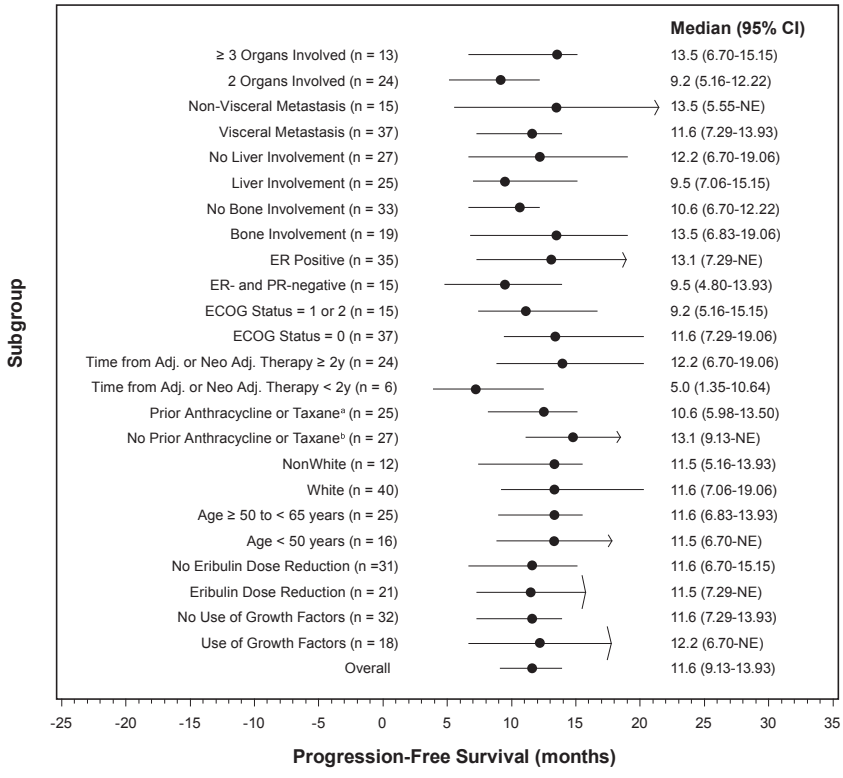


Abbreviation: NE = not estimable.

Treatment-emergent AEs led to dose adjustment (interruption/delay, reduction, or discontinuation/withdrawal) of either eribulin, trastuzumab, or both, in 36 (69.2%) patients. Specifically, TEAEs led to withdrawal of 1 or both study drugs in 11 (21.2%) patients, dose reduction in 21 (40.4%) patients, and study drug interruption in 22 (42.3%) patients. Peripheral neuropathy led to discontinuations in 7 (13.5%) patients, dose reduction in 10 (19.2%) patients, and dose interruption in 5 (9.6%) patients. Neutropenia led to dose reductions in 6 (11.5%) patients and dose interruptions in 11 (21.2%) patients, but it did not lead to any discontinuations.

Serious TEAEs occurred in 15 patients (28.8%). Neutropenia (all Grades) occurred in 8 (15.4%) patients, febrile neutropenia (all Grades) in 4 (7.7%), peripheral neuropathy (SMQ term) in 4 (7.7%), and vomiting in 3 (5.8%). There was 1 death during the study. A 59-year-old white patient died from chronic heart failure 15 days after her last dose of study treatment, after a total treatment duration of 274 days. At baseline, the patient was receiving amlodipine, furosemide, atorvastin, losartan, and atenolol, and medications for diabetes. Medical and surgical history included arteriosclerosis of the coronary artery, coronary artery bypass, diabetes mellitus, hyperlipidemia, and hypertension. The patient had NYHA Class I, ECOG was 0, and her LVEF values at baseline were normal. Her LVEF evaluations at screening, baseline, and cycle 12, day 1 were 71%, 71%, and 55%, respectively. The patient did not meet the criteria for exclusion which were clinically significant cardiovascular impairment (ie, history of congestive heart failure greater than NYHA Class II, unstable/active angina or myocardial infarction $\leq$ 6 months before day 1 of this study, or

Figure 3 Forest Plot of Subgroup Analyses



Abbreviations: Adj = adjuvant; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; NE = not estimable; Neo Adj = neoadjuvant; PR = progesterone receptor.
[a] For all patients in the full analysis set.
[b] For full analysis set patients with previous adjuvant or neoadjuvant therapies.

Table 3 Treatment-Emergent Adverse Events (All Grades in > 10% of Patients, or Grades 3/4/5 in > 5% of Patients)

TEAE	All Grades (n = 52)	Grades 3/4/5 (n = 52)
Alopecia	46 (88.5)	NA
Fatigue	36 (69.2)	4 (7.7)
Peripheral Neuropathy[a]	36 (69.2)	14 (26.9)
Neutropenia	31 (59.6)	20 (38.5)
Nausea	24 (46.2)	2 (3.8)
Diarrhea	17 (32.7)	2 (3.8)
Anemia	13 (25.0)	1 (1.9)
Constipation	13 (25.0)	0
Decreased Appetite	13 (25.0)	0
Dysgeusia	12 (23.1)	0
Edema, Peripheral	12 (23.1)	0
Pyrexia	12 (23.1)	1 (1.9)
Vomiting	12 (23.1)	3 (5.8)
Dyspepsia	10 (19.2)	2 (3.8)
Headache	10 (19.2)	2 (3.8)
Leukopenia	9 (17.3)	3 (5.8)
Stomatitis	9 (17.3)	0
Dizziness	8 (15.4)	0
Back Pain	8 (15.4)	0
Chills	8 (15.4)	1 (1.9)
Lacrimation Increased	8 (15.4)	0
Bone Pain	7 (13.5)	0
Dyspnea	7 (13.5)	1 (1.9)
Insomnia	7 (13.5)	0
Muscle Spasms	7 (13.5)	0
Oropharyngeal Pain	7 (13.5)	0
Urinary Tract Infection	7 (13.5)	1 (1.9)
Abdominal Pain	6 (11.5)	0
Depression	6 (11.5)	0
Weight Decreased	6 (11.5)	0
Febrile Neutropenia	4 (7.7)	4 (7.7)
Hyperglycemia	3 (5.8)	3 (5.8)

Data are presented as n (%).
Abbreviation: NA = not applicable; TEAE = treatment-emergent adverse event.
[a]Peripheral neuropathy includes the following preferred terms: neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paresthesia.

serious cardiac arrhythmia). The death was considered to be possibly related to the study drug by the treating investigator.

Grade 3/4 clinical laboratory hematologic abnormalities included leukocytes (23.1%; n = 12), neutrophils (55.8%; n = 29), and lymphocytes (2.2%; n = 1). Grade 3/4 clinical chemistry abnormalities included increases in alanine aminotransferase (2.0%; n = 1), sodium (3.8%; n = 2), potassium (3.8%; n = 2), phosphorus (4.0%; n = 2), and calcium (1.9%; n = 1).

One subject (1.9%) with normal baseline ECG and 3 subjects (5.8%) with clinically nonsignificant abnormal ECG findings at baseline had clinically significant abnormal findings during the study. The median change from baseline to end of treatment for LVEF was −5.0%. The 3 patients with Grade 2 LVEF decrease had trastuzumab dose delay.

Discussion

The results of this phase II trial suggest the combination of eribulin with trastuzumab has considerable activity with an acceptable toxicity profile as first-line therapy for HER2+ locally advanced or metastatic breast cancer. Results for the 52 patients evaluated in this phase II, single-arm study indicated ORR in 37 (71.2%) patients. The median DOR was 11.1 months and the median PFS was 11.6 months. The most common Grade 3/4 TEAEs (occurring in ≥ 5% of patients) were neutropenia (38.5%; n = 20), peripheral neuropathy (26.9%; n = 14, all Grade 3 [SMQ]), fatigue (7.7%; n = 4), febrile neutropenia (7.7%; n = 4), vomiting (5.8%; n = 3), leucopenia (5.8%; n = 3), and hyperglycemia (5.8%; n = 3).

Guidelines currently recommend pertuzumab with trastuzumab in combination with a taxane as a preferred option for first-line treatment of patients with HER2+ MBC.[6] Other first-line treatment regimens for HER2+ tumors include HER2+ blockading treatments such as trastuzumab with chemotherapy.[6] The activity demonstrated for eribulin with trastuzumab as first-line treatment for women with HER2+ locally advanced or metastatic breast cancer in the present study appears comparable with that reported for other chemotherapy combinations evaluated in this setting. Along with lapatinib, 4 chemotherapeutic agents are currently recommended in combination with trastuzumab as first-line treatment for patients with HER2+ MBC: docetaxel, vinorelbine, capecitabine, and paclitaxel with or without carboplatin.[6] Results for trastuzumab with docetaxel have indicated PFS ranging from 8.3 to 12.4 months and ORR ranging from 45% to 64%.[25-28] Results for vinorelbine with trastuzumab are generally similar to those that have been reported for docetaxel. One study that compared vinorelbine combined with trastuzumab and docetaxel combined with trastuzumab reported PFS of 15.3 and 12.4 months, respectively, and an ORR of 59.3% in both arms.[27] A second study that combined oral or I.V. vinorelbine with trastuzumab reported PFS of 9.3 months and an ORR of 70.3%.[7] The combination of trastuzumab and capecitabine has been shown to result in PFS of 7.8 to 9.3 months and an ORR of 38% to 65% in patients with HER2+ MBC.[10,29] Results for the combination of trastuzumab and paclitaxel indicated PFS ranging from 7.1 to 12.3 months and ORR of 36% to 75%.[30-32] A PFS of 10.7 months and an ORR of 52% have been reported for the combination of trastuzumab with paclitaxel and carboplatin.[32]

The activity of eribulin with trastuzumab appears comparable with that of other combinations currently recommended for HER2+ MBC. Although incidence rates vary, peripheral neuropathy is a common AE in patients treated with microtubule-targeted agents occurring in up to 30% of patients.[33] Peripheral neuropathy Grade 3/4 also occurs frequently in patients treated with eribulin. In the phase 3 EMBRACE trial, 35% of eribulin-treated patients had neuropathy, but < 9% had Grade 3/4 neuropathy.[23] In the present study, 36 (69.2%) patients experienced neuropathy, and 14 (26.9%) experienced Grade 3 neuropathy; no Grade 4 neuropathy was observed. This higher rate of Grade 3 neuropathy was likely due to the prolonged duration of eribulin treatment in this first-line setting.

In phase II and III trials in which patients with HER2+ MBC received microtubule-targeting agents as first-line treatment, rates of Grade 3/4 febrile neutropenia ranged from 10.1% to 37.4%.[25-28]

High rates of Grade 3/4 neutropenia were often reported particularly in combination trials of docetaxel and trastuzumab. Across several trials, rates of Grade 3/4 neutropenia ranged from 32.0% to 61.1%.[25-28] With other treatment combinations in similar patient populations, high rates of Grade 3/4 neutropenia also occurred: Andersson et al reported 41.5% in patients receiving vinorelbine and trastuzumab and in a phase III trial,[27] Robert et al reported 27% of patients receiving trastuzumab and paclitaxel and 57% receiving carboplatin with trastuzumab and paclitaxel reported Grade 3/4 neutropenia.[32] In the current trial, all Grades of febrile neutropenia and neutropenia occurred in 4 (7.7%) and 31 (59.6%) patients and Grade 3/4 was reported in 4 (7.7%) and 20 (38.5%) patients, respectively.

The duration of treatment (patients received 10.0 cycles [median] of eribulin treatment) could have contributed to cumulative neuropathic toxicity; notably, the median time to onset of treatment-emergent Grade 3/4 peripheral neuropathy was 568 days and the median duration of treatment-emergent peripheral neuropathy was 155 days for any Grade and 23 days for Grade 3/4. Although dose reductions were caused mostly by neutropenia and peripheral neuropathy, patients who received a modified dose achieved greater tumor response rates (ie, ORR, DCR, CBR, and durable stable disease) compared with those who did not. Thus, patients continued to derive clinical benefit from eribulin regardless of whether dose was reduced or maintained.

A recent systematic review of clinical studies of patients with MBC indicated that Grade 3/4 peripheral sensory neuropathy might occur in as many as 30.9% of patients treated with docetaxel and 33% of those treated with paclitaxel.[34] Analysis of phase II/III studies of ixabepilone in patients with pretreated MBC indicated that Grade 3/4 peripheral sensory neuropathy might occur in approximately 20% of patients.[35] The suggested clinical differences between eribulin and other microtubule-targeted agents are consistent with results from an experimental animal study that indicated eribulin had no effects on caudal and digital nerve conduction velocity and amplitude, compared with significant reductions in both of these measures with paclitaxel and ixabepilone. Eribulin caused mild changes in the structure of the sciatic nerve and dorsal root ganglion cells, compared with moderate-to-severe degenerative changes for paclitaxel and ixabepilone.[36]

Neuropathic symptoms resulting from treatment can cause treatment delays, dose reductions, or even discontinuation of therapy, and reduced QoL, and might interfere with activities of daily living, all of which can affect outcomes and compromise survival.[37]

Although rigorous studies on the assessment, prevention, and management of cancer treatment-related neuropathy are limited, guidelines suggest that physicians actively query cancer patients on signs and symptoms of neuropathy, especially considering that underestimation and underreporting of symptoms is common.[37] Patient history should include associated comorbidity, including inquiring about diabetes history or history of sensory neuropathy, personal and family history of neuropathy, alcohol use and other toxic exposures, and any neuropathy experienced during previous treatment.[37] A detailed treatment profile should be described (regimen dosage, duration, schedule, coasting), and the characteristics and distribution of signs and symptoms.[37] Recommended physician-based grading systems include the National Cancer Institute CTCAE,[38] Ajani Sensory,[39] World Health Organization,[40] and ECOG systems.[41]

Because neuropathy often progresses with dose accumulation, early reporting of mild cases is important when detecting the onset of neuropathy during continuous monitoring.[37] To that end, guidelines recommend using the following pain assessment tools to assess neuropathic symptoms: Brief Pain Inventory,[42,43] Neuropathic Pain Scale,[44,45] and Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale,[46,47] for the identification and assessment of functional deficits associated with neuropathy.[37]

Conclusion

In this multicenter, phase II, single-arm study, the efficacy and safety of eribulin with trastuzumab as first-line therapy for HER2+ MBC were assessed in 52 patients and showed an ORR of 71.2% (n = 37), DOR of 11.1 months, and a median PFS of 11.6 months. The most common Grade 3/4 TEAEs (occurring in ≥ 5% of patients) were neutropenia (38.5%; n = 20), peripheral neuropathy (21.2%, n = 11; all Grade 3), fatigue (7.7%; n = 4), febrile neutropenia (7.7%; n = 4), vomiting (5.8%; n = 3), leucopenia (5.8%; n = 3), and hyperglycemia (5.8%; n = 3).

The combination of eribulin with trastuzumab as first-line therapy for HER2+ MBC resulted in higher objective response and CBRs, and a prolonged median PFS with an acceptable safety profile similar to other single agents that have been commonly combined with trastuzumab as first-line therapy. Combined eribulin and trastuzumab is an acceptable treatment option for patients with HER2+ MBC.

Clinical Practice Points

- The prognosis for patients with MBC at initial diagnosis is poor, with an estimated 5-year survival rate of 24.3%.[1]
- Approximately 22% (range, 9%-74%) of patients with breast cancer have tumors that are positive for HER2,[3] and the frequency of HER2-positivity is increased among patients with metastatic disease.[4]
- The EMBRACE study demonstrated improved survival and acceptable tolerability after eribulin treatment for advanced breast cancer in patients with at least 2 previous therapies.[23]
- Eribulin has a short infusion time and requires no premedication to prevent hypersensitivity.[23]
- Assessment of eribulin in the first-line setting for women with MBC was warranted, because of its ease of use and its antitumor activity in the challenging setting of late-line treatment.
- The objective of this phase 2 trial was to assess the antitumor activity and safety of eribulin in combination with trastuzumab as first-line therapy for patients with locally recurrent or metastatic HER2+ breast cancer.
- Results for the 52 patients evaluated in this phase II, single-arm study indicated ORR in 71.2%. The median DOR was 11.1 months and the median PFS was 11.6 months. The most common Grade 3/4 TEAEs (occurring in ≥ 5% of patients) were neutropenia (38.5%), peripheral neuropathy (21.2%, all Grade 3), fatigue (7.7%), febrile neutropenia (7.7%), vomiting (5.8%), hyperglycemia (5.8%), and leucopenia (5.8%).
- The results presented here suggest the combination of eribulin with trastuzumab has considerable activity with an acceptable toxicity profile as first-line therapy for HER2+ locally advanced or metastatic breast cancer.

Acknowledgments

Funding to support this study and the preparation of this report was provided by Eisai Inc.

The authors thank Maura Dickler, Erica Mayer, Antoinette Tan, Kevin Kalinsky, and Weichung Joseph Shih of the Data Safety Monitoring Board for all their substantial contributions to this study and Leonard Lionnet, PhD, of MedVal Scientific Information Services, LLC, for providing medical writing and editorial assistance. This article was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: The GPP2 Guidelines."

Disclosure

Dr Wilks, Speaker's Bureau for Eisai Inc; Dr Puhalla, Consultant for Celldex, Medimmune, and Pfizer; Dr O'Shaughnessy, consultant to Eisai Inc; Dr Schwartzberg, research support from Eisai Inc, and consultant to Eisai Inc; Drs Berrak, Song, and Cox, employees of Eisai Inc; and Dr Vahdat, Speaker's Bureau and consultant to Eisai Inc.

References

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER Stat Fact Sheets: Breast. Available at: http://seer.cancer.gov/statfacts/html/breast.html. Accessed January 14, 2014.
2. American Cancer Society. Breast Cancer Facts and Figures 2013-2014. Available at: http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-042725.pdf. Accessed February 10, 2014.
3. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER2 therapy and personalized medicine. *Oncologist* 2009; 14:320-68.
4. Lund MJ, Butler EN, Hair BY, et al. Age/race differences in HER2 testing and in incidence rates for breast cancer triple subtypes: a population-based study and first report. *Cancer* 2010; 116:2549-59.
5. Valabrega G, Montemurro F, Aglietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer. *Ann Oncol* 2007; 18:977-84.
6. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Breast Cancer*. Fort Washington, PA: National Comprehensive Cancer Network; 2014.
7. Heinemann V, Di Gioia D, Vehling-Kaiser U, et al. A prospective multicenter phase II study of oral and i.v. vinorelbine plus trastuzumab as first-line therapy in HER2-overexpressing metastatic breast cancer. *Ann Oncol* 2011; 22:603-8.
8. Redana S, Donadio M, Nole F, et al. Trastuzumab with either docetaxel or vinorelbine as first-line treatment for patients with HER2-positive advanced breast cancer: a retrospective comparison. *BMC Cancer* 2010; 10:28.
9. Wardley AM, Pivot X, Morales-Vasquez F, et al. Randomized phase II trial of first-line trastuzumab plus docetaxel and capecitabine compared with trastuzumab plus docetaxel in HER2-positive metastatic breast cancer. *J Clin Oncol* 2010; 28: 976-83.
10. Michalaki V, Fotiou S, Gennatas S, Gennatas C. Trastuzumab plus capecitabine and docetaxel as first-line therapy for HER2-positive metastatic breast cancer: phase II results. *Anticancer Res* 2010; 30:3051-4.
11. Chan A, Conte PF, Petruzelka L, et al. Phase II study of a triple combination of oral vinorelbine, capecitabine and trastuzumab as first-line treatment in HER2-positive metastatic breast cancer. *Anticancer Res* 2013; 33:2657-64.
12. Inoue K, Nakagami K, Mizutani M, et al. Randomized phase III trial of trastuzumab monotherapy followed by trastuzumab plus docetaxel versus trastuzumab plus docetaxel as first-line therapy in patients with HER2-positive metastatic breast cancer: the JO17360 Trial Group. *Breast Cancer Res Treat* 2010; 119:127-36.
13. Tonyali O, Benekli M, Berk V, et al. Efficacy and toxicity of trastuzumab and paclitaxel plus capecitabine in the first-line treatment of HER2-positive metastatic breast cancer. *J Cancer Res Clin Oncol* 2013; 139:981-6.
14. Tan WW, Allred JB, Salim M, et al. Phase II interventional study (N0337) of capecitabine in combination with vinorelbine and trastuzumab for first- or second-line treatment of HER2-positive metastatic breast cancer: a North Central Cancer Treatment Group trial. *Clin Breast Cancer* 2012; 12:81-6.
15. Moulder S, Li H, Wang M, et al. A phase II trial of trastuzumab plus weekly ixabepilone and carboplatin in patients with HER2-positive metastatic breast cancer: an Eastern Cooperative Oncology Group Trial. *Breast Cancer Res Treat* 2010; 119:663-71.
16. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012; 366:109-19.
17. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; 365:1273-83.
18. Jordan MA, Kamath K, Manna T, et al. The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. *Mol Cancer Ther* 2005; 4:1086-95.
19. Okouneva T, Azarenko O, Wilson L, Littlefield BA, Jordan MA. Inhibition of centromere dynamics by eribulin (E7389) during mitotic metaphase. *Mol Cancer Ther* 2008; 7:2003-11.
20. Smith JA, Wilson L, Azarenko O, et al. Eribulin binds at microtubule ends to a single site on tubulin to suppress dynamic instability. *Biochemistry* 2010; 49: 1331-7.
21. Jordan MA, Kamath K. How do microtubule-targeted drugs work? An overview. *Curr Cancer Drug Targets* 2007; 7:730-42.
22. Jain S, Cigler T. Eribulin mesylate in the treatment of metastatic breast cancer. *Biologics* 2012; 6:21-9.
23. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 2011; 377:914-23.
24. *Halaven (eribulin mesylate) injection [prescribing information]*. Woodcliff Lake, NJ: Eisai Inc; 2013.
25. Hurvitz SA, Dirix L, Kocsis J, et al. Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol* 2013; 31: 1157-63.
26. Servitja S, Ramos M, Gil M, et al. Multicenter, phase II, nonrandomized study of docetaxel plus trastuzumab every 21 days as the primary therapy in metastatic breast cancer overexpressing HER2. *Anticancer Drugs* 2012; 23:239-46.
27. Andersson M, Lidbrink E, Bjerre K, et al. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. *J Clin Oncol* 2011; 29:264-71.
28. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005; 23:4265-74.
29. Yamamoto D, Iwase S, Kitamura K, Odagiri H, Yamamoto C, Nagumo Y. A phase II study of trastuzumab and capecitabine for patients with HER2-overexpressing metastatic breast cancer: Japan Breast Cancer Research Network (JBCRN) 00 Trial. *Cancer Chemother Pharmacol* 2008; 61:509-14.
30. Fountzilas G, Tsavdaridis D, Kalogera-Fountzila A, et al. Weekly paclitaxel as first-line chemotherapy and trastuzumab in patients with advanced breast cancer. A Hellenic Cooperative Oncology Group phase II study. *Ann Oncol* 2001; 12: 1545-51.
31. Gasparini G, Gion M, Mariani L, et al. Randomized Phase II Trial of weekly paclitaxel alone versus trastuzumab plus weekly paclitaxel as first-line therapy of patients with HER2 positive advanced breast cancer. *Breast Cancer Res Treat* 2007; 101:355-65.
32. Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2006; 24: 2786-92.
33. Lee JJ, Swain SM. Peripheral neuropathy induced by microtubule-stabilizing agents. *J Clin Oncol* 2006; 24:1633-42.
34. Smith EM. Current methods for the assessment and management of taxane-related neuropathy. *Clin J Oncol Nurs* 2013; 17(suppl):22-34.
35. Vahdat LT, Thomas ES, Roche HH, et al. Ixabepilone-associated peripheral neuropathy: data from across the phase II and III clinical trials. *Support Care Cancer* 2012; 20:2661-8.
36. Wozniak KM, Nomoto K, Lapidus RG, et al. Comparison of neuropathy-inducing effects of eribulin mesylate, paclitaxel, and ixabepilone in mice. *Cancer Res* 2011; 71:3952-62.
37. Stubblefield MD, Burstein HJ, Burton AW, et al. NCCN task force report: management of neuropathy in cancer. *J Natl Compr Cancer Network* 2009; 7(suppl 5):S1-26.
38. National Cancer Institute. Common Terminology Criteria for Adverse Events v3.0. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed April 8, 2014.
39. Ajani JA, Welch SR, Raber MN, Fields WS, Krakoff IH. Comprehensive criteria for assessing therapy-induced toxicity. *Cancer Invest* 1990; 8:147-59.
40. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; 47:207-14.
41. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5:649-55.
42. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994; 23:129-38.
43. Tittle MB, McMillan SC, Hagan S. Validating the brief pain inventory for use with surgical patients with cancer. *Oncol Nurs Forum* 2003; 30:325-30.
44. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. *Neurology* 1997; 48:332-8.
45. Jensen MP, Friedman M, Bonzo D, Richards P. The validity of the neuropathic pain scale for assessing diabetic neuropathic pain in a clinical trial. *Clin J Pain* 2006; 22:97-103.
46. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain* 2001; 92:147-57.
47. Potter J, Higginson IJ, Scadding JW, Quigley C. Identifying neuropathic pain in patients with head and neck cancer: use of the Leeds Assessment of Neuropathic Symptoms and Signs Scale. *J R Soc Med* 2003; 96:379-83.