Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study

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Summary

Background Treatments with survival benefit are greatly needed for women with heavily pretreated metastatic breast cancer. Eribulin mesilate is a non-taxane microtubule dynamics inhibitor with a novel mode of action. We aimed to compare overall survival of heavily pretreated patients receiving eribulin versus currently available treatments.

Methods In this phase 3 open-label study, women with locally recurrent or metastatic breast cancer were randomly allocated (2:1) to eribulin mesilate (1·4 mg/m² administered intravenously during 2–5 min on days 1 and 8 of a 21-day cycle) or treatment of physician's choice (TPC). Patients had received between two and five previous chemotherapy regimens (two or more for advanced disease), including an anthracycline and a taxane, unless contraindicated. Randomisation was stratified by geographical region, previous capecitabine treatment, and human epidermal growth factor receptor 2 status. Patients and investigators were not masked to treatment allocation. The primary endpoint was overall survival in the intention-to-treat population. This study is registered at ClinicalTrials.gov, number NCT00388726.

Findings 762 women were randomly allocated to treatment groups (508 eribulin, 254 TPC). 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=0·041). The most common adverse events 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). Peripheral neuropathy was the most common adverse event leading to discontinuation from eribulin, occurring in 24 (5%) of 503 patients.

Interpretation Eribulin showed a significant and clinically meaningful improvement in overall survival compared with TPC in women with heavily pretreated metastatic breast cancer. This finding challenges the notion that improved overall survival is an unrealistic expectation during evaluation of new anticancer therapies in the refractory setting.

Funding Eisai.

Introduction

A great need exists for treatments that improve overall survival for women with advanced or recurrent metastatic breast cancer, particularly those with heavily pretreated disease. Many patients either do not respond or become refractory to agents such as anthracyclines and taxanes.[1,2] There is then no single standard of care for such women, and at the time of this study the only cytotoxics approved as monotherapy in this setting were capecitabine and ixabepilone (for patients also resistant to capecitabine; approved in the USA and some other countries on the basis of phase 2 data). Neither capecitabine nor ixabepilone has, however, been investigated in adequately powered single-agent studies assessing survival benefit.

Eribulin mesilate (E7389) is a non-taxane inhibitor of microtubule dynamics of the halichondrin class of antineoplastic drugs. It is a structurally modified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*. Eribulin has a novel mode of action that is distinct from those of other tubulin-targeting agents,[3–7] inhibiting the microtubule growth phase without affecting the shortening phase, and causing tubulin sequestration into non-productive aggregates. In preclinical studies, eribulin induced less neuropathy than did paclitaxel[8] and retained activity in cell lines that were resistant to paclitaxel through β-tubulin mutations.[9] Eribulin could therefore be effective in patients with disease that is resistant to other tubulin-targeting agents.

In phase 1[10–12] and phase 2 studies[13,14] eribulin was active, with a predictable side-effect profile, in patients with extensively pretreated locally advanced or metastatic breast cancer. Patients in both phase 2 studies (n=103[13] and n=299[14]) had received a median of four previous chemotherapy regimens; objective response rates were 11·5% (ten of 87 patients in the per-protocol population;

95% CI 5·7–20·1) and 9·3% (25 of 269 in the eligible population; 95% CI 6·1–13·4), and median overall survival was 9·0 and 10·4 months, respectively.

In this phase 3 study, we aimed to compare overall survival of women with heavily pretreated metastatic breast cancer receiving eribulin or real-life treatment choices. A distinctive comparator group, treatment of physician's choice (TPC), represented a mix of agents (both approved and non-approved for metastatic breast cancer) to mirror clinical practice at the time in this setting.

Methods

Study design and patients

The EMBRACE trial (study E7389-G000-305) was a phase 3, global, multicentre, randomised, open-label study of eribulin versus TPC in women with heavily pretreated locally recurrent or metastatic breast cancer. Key inclusion criteria were: age 18 years or older; histologically or cytologically confirmed breast cancer with measurable or evaluable disease; between two and five previous chemotherapy regimens, including an anthracycline and a taxane, and two or more regimens for locally recurrent or metastatic breast cancer; progression within 6 months or less of latest chemotherapy; adequate bone marrow, liver, and renal function; an Eastern Cooperative Oncology Group performance status of 0–2; and life expectancy of 3 months or more. Key exclusion criteria were: previous participation in an eribulin trial; use of any investigational drug within 4 weeks of the study; treatment with chemotherapy, radiation, trastuzumab, or hormone therapy within 3 weeks of the study; known brain metastases unless treated and stable; and pre-existing neuropathy of grade higher than 2.

All patients provided written informed consent, and study approval was obtained from ethics committees. The study was undertaken in accordance with the World Medical Association (WMA) Declaration of Helsinki revised edition (WMA General Assembly, Tokyo, 2004), the International Conference for Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use, good clinical practice (CPMP/ICH/135/95), the European Clinical Trial Directive 2001/20/EC, and local ethical and legal requirements. An independent data monitoring committee reviewed safety and interim efficacy data.

Randomisation and masking

Each patient was assessed for eligibility and then their proposed TPC was chosen and confirmed before randomisation. Patients were randomised centrally by an interactive voice recognition system to receive eribulin or TPC. A 2:1 ratio was used to increase the appeal of the study to patients and investigators. Randomisation was stratified to ensure balance between treatment groups within the following strata levels: geographical region (North America/western Europe/Australia [region 1]; eastern Europe [region 2]; and Latin America/South Africa [region 3]), previous capecitabine treatment, and human epidermal growth factor receptor 2 (HER2, also

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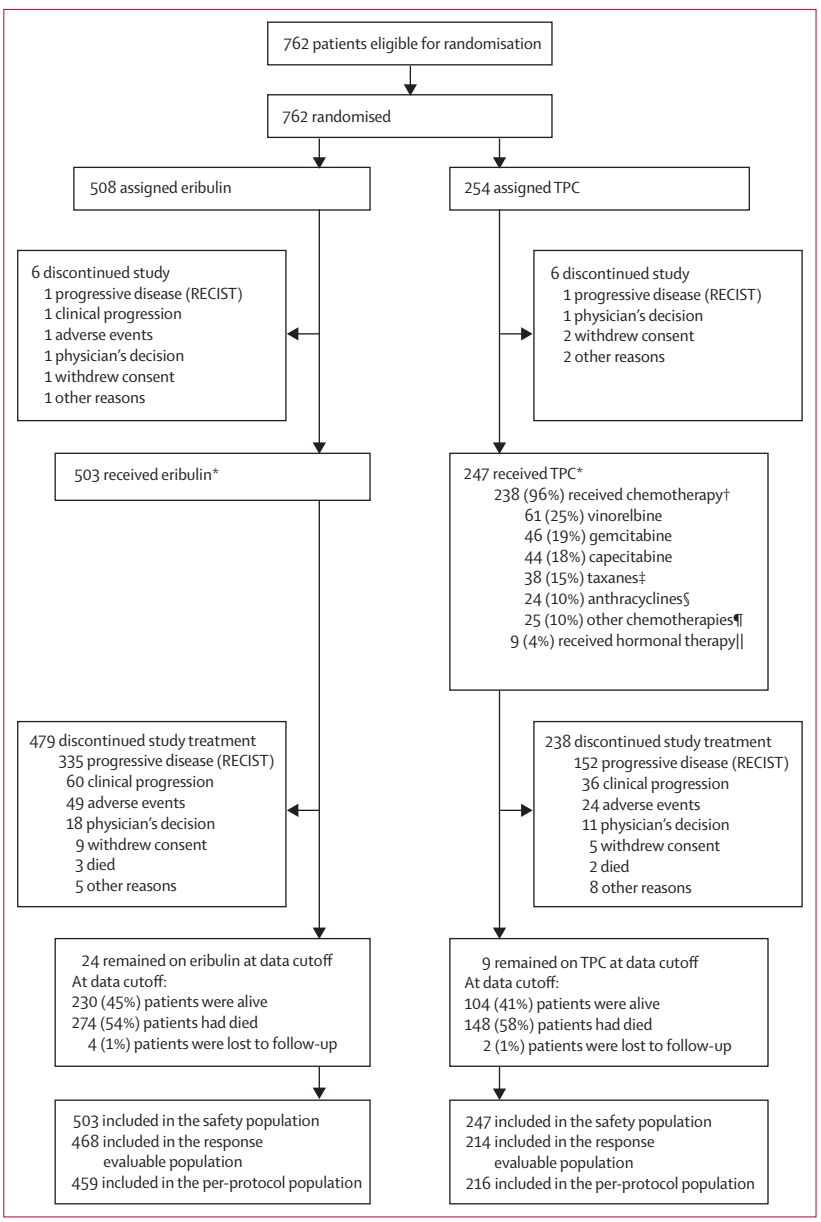

Figure 1: **Trial profile**
RECIST=Response Evaluation Criteria in Solid Tumours.[15] TPC=treatment of physician's choice. *One patient was randomly allocated TPC, but returned and was rescreened and rerandomised to eribulin; this patient is included in the TPC group in the intention-to-treat population, excluded from the per-protocol population, and included in the eribulin group in the safety population. †Two patients received more than one TPC: one patient received gemcitabine and paclitaxel (and was included in the gemcitabine group because she was randomly assigned to gemcitabine), and one patient received cyclophosphamide and methotrexate; one patient was assigned to chemotherapy, but received hormonal treatment. ‡21 patients received paclitaxel (but one patient received paclitaxel in combination with gemcitabine and was included in the gemcitabine group, not the taxane group), ten patients received docetaxel, five patients received nab-paclitaxel, and three patients received ixabepilone. §19 patients received doxorubicin, four patients received liposomal doxorubicin, and one patient received mitoxantrone. ¶Other chemotherapies were: cisplatin (n=9), carboplatin (n=4), cyclophosphamide (n=4), etoposide (n=4), mitomycin (n=3), fluorouracil (n=1), and methotrexate (n=1). ||Hormonal therapies were: fulvestrant (n=4), letrozole (n=3), exemestane (n=1), and tamoxifen (n=1).

	Eribulin (n=508)	TPC (n=254)	Overall (n=762)
Age (years)	55·0 (28–85)	56·0 (27–81)	55·0 (27–85)
Ethnic origin			
White	470 (93%)	233 (92%)	703 (92%)
Black	20 (4%)	14 (6%)	34 (4%)
Asian/Pacific Islander	3 (1%)	2 (1%)	5 (1%)
Other	15 (3%)	5 (2%)	20 (3%)
Geographical region			
North America/western Europe/Australia	325 (64%)	163 (64%)	488 (64%)
Eastern Europe	129 (25%)	64 (25%)	193 (25%)
Latin America/South Africa	54 (11%)	27 (11%)	81 (11%)
ECOG performance status			
0	217 (43%)	103 (41%)	320 (42%)
1	244 (48%)	126 (50%)	370 (49%)
2	39 (8%)	22 (9%)	61 (8%)
HER2 (combined FISH and IHC tests)*			
Positive	83 (16%)	40 (16%)	123 (16%)
Negative	373 (73%)	192 (76%)	565 (74%)
Unknown	4 (1%)	0	4 (1%)
Not done	48 (9%)	22 (9%)	70 (9%)
OR and PgR status			
OR and/or PgR positive	327 (64%)	162 (64%)	489 (64%)
OR and PgR negative	124 (24%)	63 (25%)	187 (25%)
Unknown	57 (11%)	29 (11%)	86 (11%)
OR, PgR, HER2 negative	93 (18%)	51 (20%)	144 (19%)
Most common metastatic sites			
Bone	306 (60%)	158 (62%)	464 (61%)
Liver	296 (58%)	159 (63%)	455 (60%)
Lymph nodes	220 (43%)	118 (46%)	338 (44%)
Lung	197 (39%)	95 (37%)	292 (38%)
Number of organs involved			
1	85 (17%)	35 (14%)	120 (16%)
2	172 (34%)	82 (32%)	254 (33%)
3	145 (29%)	77 (30%)	222 (29%)
≥4	104 (20%)	60 (24%)	164 (22%)
Number of previous chemotherapy regimens†			
1	1 (<1%)	0	1 (<1%)
2	65 (13%)	31 (12%)	96 (13%)
3	176 (35%)	83 (33%)	259 (34%)
4	166 (33%)	79 (31%)	245 (32%)
5	85 (17%)	51 (20%)	136 (18%)
≥6	13 (3%)	9 (4%)	22 (3%)
Median	4 (1–7)	4 (2–7)	4 (1–7)
Previous chemotherapy‡			
Taxanes	503 (99%)	251 (99%)	754 (99%)
Anthracyclines	502 (99%)	250 (98%)	752 (99%)
Capecitabine	370 (73%)	189 (74%)	559 (73%)
Refractory to§			
Taxane	410 (81%)	204 (80%)	614 (81%)
Capecitabine	342 (67%)	174 (69%)	516 (68%)
Anthracycline	284 (56%)	156 (61%)	440 (58%)
Previous surgery	436 (86%)	216 (85%)	652 (86%)
Previous radiotherapy	420 (83%)	195 (77%)	615 (81%)

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known as ERBB2) status before randomisation. Stratification factors were chosen in part to reflect regional differences in drug availability and medical practice. Patients and investigators were not masked to treatment allocation.

Procedures

Patients received eribulin mesilate (1·4 mg/m² administered intravenously during 2–5 min on days 1 and 8 of a 21-day cycle) or TPC (defined as any single-agent chemotherapy or hormonal or biological treatment approved for the treatment of cancer and to be administered according to local practice; radiotherapy; or symptomatic treatment alone). Treatment continued until disease progression, unacceptable toxic effects, patient or physician request to discontinue, or serious protocol non-compliance. Grade 3 or 4 toxic effects were managed by dose modifications. Concomitant treatments that did not interfere with the evaluation of eribulin (or were allowed with the relevant TPC agent) could be given at the investigator's discretion, including palliative radiotherapy, but excluding other investigational antitumour treatments.

The primary objective was to compare overall survival between the two treatment groups; secondary objectives were to compare progression-free survival, objective response rates, and duration of response. We defined overall survival from date of randomisation to death or to last date known alive (censored). Progression-free survival was assessed from randomisation to the earliest date of disease progression or death (from any cause), or censored (as for overall survival). Progression-free survival, objective response rate, and duration of response were based on independent masked review of tumour assessments. We also did sensitivity analyses of these assessments on the basis of the investigator's review.

Tumour response was assessed (with Response Evaluation Criteria in Solid Tumours [RECIST][15]) every 8 weeks (within 1 week), or sooner if disease progression was suspected. Complete or partial responses needed confirmation 4 weeks or more later. Patients with complete or partial responses or stable disease withdrawing from treatment before disease progression continued tumour assessments every 3 months until progressive disease or commencement of new anticancer treatment. Duration of response was defined as the time from first documented response until disease progression, death from any cause, or date of censoring. We defined clinical benefit rate as duration of complete response, partial response, and stable disease of 6 months or longer. Safety was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Overall survival, progression-free survival, objective response rate, duration of response, and safety assessments were protocol prespecified; clinical benefit rate and exploratory subset analyses were not prespecified.

Statistical analysis

We originally planned to enrol 630 patients to achieve the 411 events (deaths) that were needed for the primary analysis. This number was later increased to a maximum of 1000 patients when the masked evaluation of the overall event rate suggested that deaths were occurring slower than expected. No change was made to the number of events needed for final analysis.

Primary analysis of overall survival included the intention-to-treat (ITT) population (all patients randomly assigned to treatment groups), with a two-sided stratified log-rank test at a nominal significance level of 0·049 (adjusted for interim analysis). We used a Cox regression model to calculate the hazard ratio (HR). Progression-free survival was analysed with similar methods to overall survival, but with a 5% significance level. Objective response rate was analysed with exact Pearson-Clopper two-sided 95% CIs in patients with measurable disease per RECIST. All analyses presented were preplanned. Summary statistics for adverse events were provided for the safety population (all patients randomly assigned to treatment groups who received either eribulin or TPC). The per-protocol population consisted of patients who met key inclusion criteria and had no major protocol violation. SAS/STAT® software (version 9.1) was used for all analyses (SAS and all other SAS Institute Inc products or service names are registered trademarks or trademarks of SAS Institute Inc in the USA and other countries; ® indicates USA registration).

This study is registered at ClinicalTrials.gov, number NCT00388726.

Role of the funding source

The study design, collection of data, analysis, and interpretation of the results were funded by Eisai. Eisai employees participated in the study design, data analysis, and interpretation. Data were obtained locally and the central study database was audited by Eisai. Independent masked review of image data was undertaken by ICON Medical Imaging (Warrington, PA, USA). Emma Robinson (Complete Medical Communications, Macclesfield, UK) provided medical writing support funded by Eisai. The corresponding author had full access to all the study data and final responsibility for the decision to submit for publication.

Results

From Nov 16, 2006, to Nov 17, 2008, 762 patients from 135 centres in 19 countries were randomly allocated to treatment groups (508 eribulin, 254 TPC; figure 1). No TPC patient received supportive care alone; most (238 [96%] of 247) received chemotherapy, which was most often vinorelbine, gemcitabine, or capecitabine (figure 1). Baseline demographic characteristics were well balanced across treatment groups (table 1). Patients were heavily pretreated (median four previous chemotherapy regimens); 559 (73%) of 762 patients had received capecitabine previously. Overall, 16% (123 of 762 patients) had HER2-positive disease, and 19% (144 patients) were triple-negative. The most common metastatic sites were bone and liver; 386 (51%) of 762 patients had metastatic disease involving three or more organs.

	Eribulin (n=508)	TPC (n=254)	Overall (n=762)
(Continued from previous page)			
Previous hormone therapy	430 (85%)	210 (83%)	640 (84%)
Number of previous hormone regimens			
1	220 (43%)	96 (38%)	316 (41%)
2	109 (21%)	65 (26%)	174 (23%)
3	60 (12%)	23 (9%)	83 (11%)
≥4	41 (8%)	26 (10%)	67 (9%)

Data are median (range) or n (%). One patient was randomly allocated to TPC, but returned and was rescreened and rerandomised to eribulin; this patient is included in the TPC group in the intention-to-treat population, excluded from the per-protocol population, and included in the eribulin group in the safety population. TPC=treatment of physician's choice. ECOG=Eastern Cooperative Oncology Group. HER2=human epidermal growth factor receptor 2. FISH=fluorescence in-situ hybridisation. IHC=immunohistochemistry. OR=oestrogen receptor. PgR=progesterone receptor. *On the basis of local laboratory testing. †Patients who had received one or six or more previous chemotherapy regimens were excluded from the per-protocol population. ‡Patients who had not previously received a taxane or an anthracycline (unless contraindicated) were excluded from the per-protocol population; three of the eight patients who had not received a taxane had a contraindication, and five of the ten patients who had not received an anthracycline had a contraindication. §Refractory was defined as those who progressed on or within 6 months of receiving treatment.

Table 1: **Demographic and baseline characteristics**

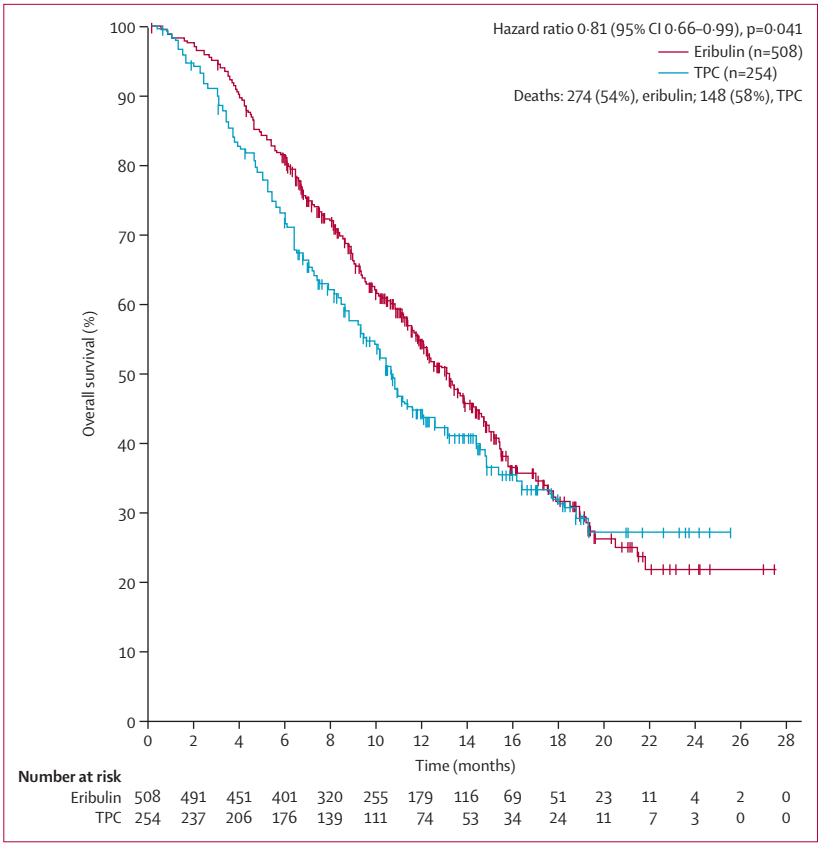

Figure 2: **Kaplan-Meier graph of overall survival**

Analysis was protocol prespecified and included the intention-to-treat population. Tickmarks show censored data. TPC=treatment of physician's choice.

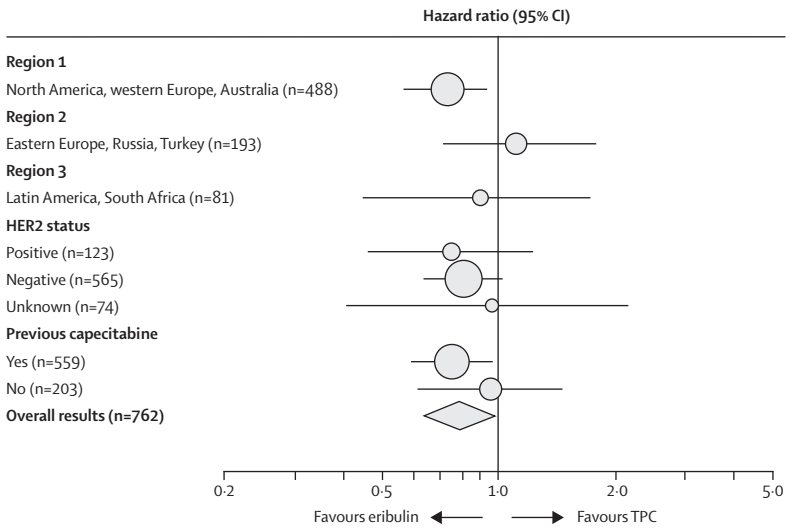

Figure 3: **Exploratory subgroup analysis of overall survival**
Analysis included the intention-to-treat population and was not protocol prespecified. Based on a stratified Cox analysis including geographical region, HER2 status, and previous capecitabine treatment as strata. HER2=human epidermal growth factor receptor 2. TPC=treatment of physician's choice.

	Independent review			Investigator review		
	Eribulin	TPC	HR* (95% CI), p value	Eribulin	TPC	HR* (95% CI), p value
Progression-free survival						
Median (months)	3·7 (3·3–3·9)	2·2 (2·1–3·4)	0·87 (0·71–1·05), p=0·137	3·6 (3·3–3·7)	2·2 (2·0–2·6)	0·76 (0·64–0·90), p=0·002
Best overall tumour response						
Tumour response						
Complete response	3 (1%)	0	..	1 (<1%)	0	..
Partial response	54 (12%)	10 (5%)	..	61 (13%)	16 (7%)	..
Stable disease	208 (44%)	96 (45%)	..	219 (47%)	96 (45%)	..
Progressive disease	190 (41%)	105 (49%)	..	176 (38%)	97 (45%)	..
Not evaluable	12 (3%)	3 (1%)	..	11 (2%)	5 (2%)	..
Unknown	1 (<1%)	0	..	0	0	..
Objective response rate†	57 (12%; 9·4–15·5)	10 (5%; 2·3–8·4)	p=0·002‡	62 (13%; 10·3–16·7)	16 (7%; 4·3–11·9)	p=0·028‡
Clinical benefit rate§	106 (23%; 18·9–26·7)	36 (17%; 12·1–22·5)	..	130 (28%; 23·8–32·1)	43 (20%; 14·9–26·1)	..

Data for progression-free survival are median (95% CI), for tumour response are n (%), and for rates of objective response and clinical benefit are n (%; exact Pearson-Clopper two-sided 95% CI). Analysis of progression-free survival included the intention-to-treat population for both reviews (eribulin, n=508; TPC, n=254); analysis of best overall tumour response included the population with measurable disease as per Response Evaluation Criteria in Solid Tumours (eribulin, n=468; TPC, n=214).[15] TPC=treatment of physician's choice. HR=hazard ratio. HER2=human epidermal growth factor receptor 2. *HRs based on a Cox model including HER2 status, previous capecitabine treatment, and geographical region as strata; analysis of progression-free survival by independent and investigator review was protocol prespecified. †Objective response rate included complete response and partial response; analysis of objective response rate by independent and investigator review was protocol prespecified. ‡Fisher's exact test. §Clinical benefit rate included complete or partial response or stable disease of at least 6 months' duration; statistical analysis of clinical benefit rate was not prespecified in the protocol and was therefore not done.

Table 2: **Progression-free survival and best overall tumour response as assessed by independent review and investigator review**

The median duration of eribulin treatment (n=503) was 3·9 months (range 0·7–16·3); 295 (59%) of 503 patients received five or more eribulin cycles (range 1–23). Median duration of TPC was 2·1 months (range 0·03–21·2) for patients receiving chemotherapy (n=238), and 1·0 month (range 0·8–6·2) with hormone therapy (n=9). Dose interruptions, delays, and reductions were undertaken in 28 (6%), 248 (49%), and 145 (29%) of 503 patients, respectively, in the eribulin group, and in 21 (9%), 98 (41%), and 63 (26%) of 238 patients, respectively, in the chemotherapy TPC group.

The study met its primary objective, showing a significant increase in overall survival for eribulin compared with TPC (HR 0·81, 95% CI 0·66–0·99; p=0·041), with 274 (54%) deaths in the eribulin group and 148 (58%) deaths in the TPC group (figure 2). Median overall survival was 13·1 months (95% CI 11·8–14·3) in patients receiving eribulin and 10·6 months (9·3–12·5) in those assigned TPC; 1-year survival rates were 53·9% in the eribulin group and 43·7% in the TPC group. Exploratory subset analysis according to stratification factors showed significantly longer overall survival in region 1 (n=488) with eribulin than with TPC (median 13·1 months [95% CI 11·8–14·9] and 10·1 months [8·4–10·9], respectively) (HR 0·72, 95% CI 0·57–0·92; p=0·009; figure 3). The HR was close to 1 for patients from regions 2 (n=193; HR 1·09, 95% CI 0·70–1·71) and 3 (n=81; HR 0·91, 0·47–1·78).

Median progression-free survival was 3·7 months (95% CI 3·3–3·9) with eribulin and 2·2 months (2·1–3·4) with TPC (HR 0·87; 95% CI 0·71–1·05; p=0·137) in the ITT population by independent review (table 2, figure 4). Median progression-free survival was similar in the investigator assessment of the ITT population, but the difference between treatment groups was significant (HR 0·76, 95% CI 0·64–0·90; p=0·002; table 2, figure 4). Fewer patients were censored with investigator review than with independent review (127 *vs* 241), resulting in more progression events in the investigator than independent review (635 *vs* 521). In the per-protocol population, median progression-free survival was similar to that of the ITT population, but the improvement with eribulin versus TPC was significant by both independent and investigator review (figure 4).

Objective response was recorded in 57 (12%) of 468 patients treated with eribulin and ten (5%) of 214 receiving TPC (p=0·002; table 2) by independent review in patients with measurable disease, including three complete responses with eribulin but none with TPC. Median duration of response for eribulin was 4·2 months (95% CI 3·8–5·0) and for TPC was 6·7 months (6·7–7·0) (p=0·159); clinical benefit rates were 23% for eribulin (106 of 468 patients) and 17% for TPC (36 of 214 patients). Results for both objective response and clinical benefit were similar by investigator review (table 2).

Adverse events occurred in 497 (99%) of 503 patients receiving eribulin and 230 (93%) of 247 patients given

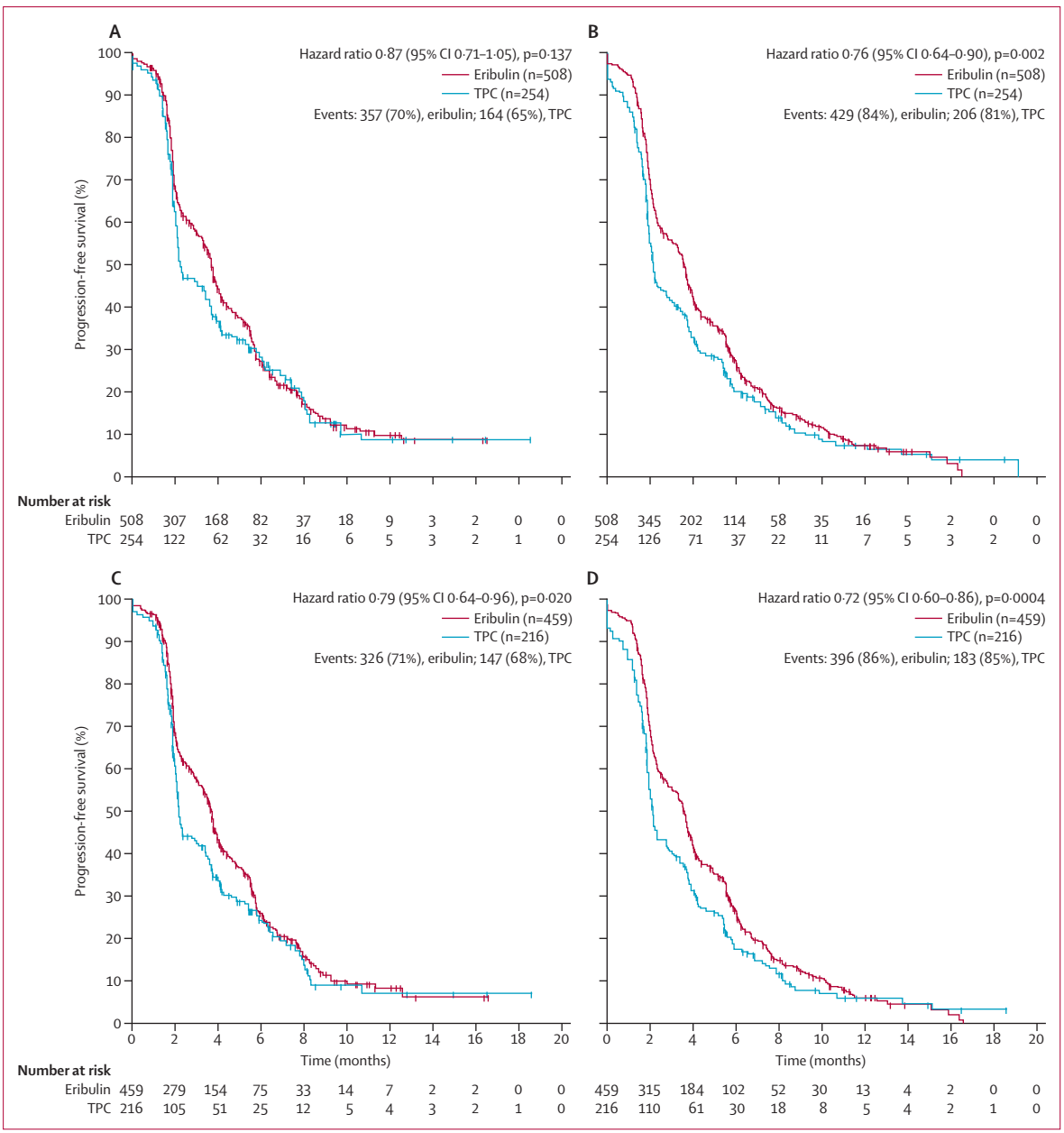

Figure 4: **Kaplan-Meier graphs of progression-free survival by (A) independent review and (B) investigator review of the intention-to-treat population, and (C) independent review and (D) investigator review of the per-protocol population**
All analyses were protocol prespecified. Tickmarks show censored data. TPC=treatment of physician's choice.

TPC. Serious adverse events occurred in 126 (25%) of patients on eribulin and 64 (26%) of those on TPC, and adverse events leading to therapy discontinuation occurred in 67 (13%) of eribulin patients and 38 (15%) of TPC patients. The most common adverse events in both groups were asthenia or fatigue and neutropenia; most adverse events were CTCAE grade 1 or 2 (table 3). Grade 3 or 4 adverse events that occurred more often with eribulin than with TPC were neutropenia, leucopenia, and peripheral neuropathy. Fatal adverse events occurred in 20 (4%) of 503 patients on eribulin and 18 (7%) of 247 patients on TPC; these events were reported as treatment-related for five (1%) patients receiving eribulin (febrile neutropenia, lung infection, and bronchopneumonia in one patient each, dyspnoea in two patients) and two (1%) patients receiving TPC (febrile neutropenia, aspergillosis in one patient each).

Neutropenia was the most common clinical grade 3 or 4 adverse event (ie, judged significant by the investigator) with eribulin (grade 3: 106 [21%] of

	Eribulin (n=503)			TPC (n=247)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Haematological						
Neutropenia†	260 (52%)	106 (21%)	121 (24%)	73 (30%)	35 (14%)	17 (7%)
Leucopenia	116 (23%)	59 (12%)	11 (2%)	28 (11%)	12 (5%)	2 (1%)
Anaemia	94 (19%)	9 (2%)	1 (<1%)	56 (23%)	8 (3%)	1 (<1%)
Non-haematological						
Asthenia/fatigue	270 (54%)	41 (8%)	3 (1%)	98 (40%)	25 (10%)	0
Alopecia	224 (45%)	..	..	24 (10%)	..	..
Peripheral neuropathy‡	174 (35%)	39 (8%)	2 (<1%)	40 (16%)	5 (2%)	0
Nausea	174 (35%)	6 (1%)	0	70 (28%)	6 (2%)	0
Constipation	124 (25%)	3 (1%)	0	51 (21%)	2 (1%)	0
Arthralgia/myalgia	109 (22%)	2 (<1%)	0	29 (12%)	3 (1%)	0
Weight loss	107 (21%)	3 (1%)	0	35 (14%)	1 (<1%)	0
Pyrexia	105 (21%)	1 (<1%)	0	31 (13%)	1 (<1%)	0
Anorexia	98 (19%)	2 (<1%)	0	32 (13%)	3 (1%)	0
Headache	97 (19%)	2 (<1%)	0	29 (12%)	0	1 (<1%)
Diarrhoea	92 (18%)	0	0	45 (18%)	0	0
Vomiting	91 (18%)	4 (1%)	1 (<1%)	44 (18%)	3 (1%)	0
Back pain	79 (16%)	3 (1%)	1 (<1%)	18 (7%)	3 (1%)	1 (<1%)
Dyspnoea	79 (16%)	18 (4%)	0	31 (13%)	6 (2%)	1 (<1%)
Cough	72 (14%)	0	0	21 (9%)	0	0
Bone pain	60 (12%)	9 (2%)	0	23 (9%)	4 (2%)	0
Pain in extremity	57 (11%)	5 (1%)	0	25 (10%)	3 (1%)	0
Mucosal inflammation	43 (9%)	7 (1%)	0	25 (10%)	5 (2%)	0
Palmar-plantar erythrodysaesthesia	7 (1%)	2 (<1%)	0	34 (14%)	9 (4%)	0

Data are n (%). TPC=treatment of physician's choice. *Safety assessments were protocol prespecified and included the safety population (all patients randomly assigned to treatment groups who received either eribulin or TPC). †Data are adverse events as reported by the investigators. ‡Peripheral neuropathy includes neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paraesthesia.

Table 3: **Adverse events with an incidence higher than 10% in either treatment group***

503 patients; grade 4: 121 [24%] of 503 patients; table 3) and in TPC subgroups of vinorelbine (grade 3: 18 [30%] of 61 patients; grade 4: six [10%] of 61 patients), taxanes (grade 3: five [13%] of 38 patients; grade 4: six [16%] of 38 patients), and gemcitabine (grade 3: nine [20%] of 46 patients; grade 4: three [7%] of 46 patients). Neutropenia was managed with dose delays, reductions, and granulocyte colony stimulating factor (given to 89 [18%] of 503 patients in the eribulin group and 19 [8%] of 247 in the TPC group). Febrile neutropenia occurred at low incidence with eribulin (23 [5%] of 503 patients) and TPC (four [2%] of 247 patients; n=1 with vinorelbine, gemcitabine, liposomal doxorubicin, and etoposide). Four (<1%) patients discontinued eribulin because of haematological adverse events. A grade 3 or 4 neutrophil count occurred in 287 (57%) of 503 eribulin patients (laboratory results); mean time to nadir within a cycle was roughly 13 days, and mean time to recovery to grade 2 or lower was roughly 8 days.

The incidence of peripheral neuropathy with eribulin (overall: 174 [35%] of 503 patients; grade 3: 39 patients [8%]; grade 4: two patients [<1%]) was similar to that in the taxane subgroup (overall: 17 [45%] of 38 patients; grade 3: two [5%] patients; no grade 4). Peripheral neuropathy was the most common adverse event leading to discontinuation from eribulin (24 [5%] of 503 patients). In patients with grade 3 or 4 peripheral neuropathy who continued treatment, neuropathy improved to grade 2 or lower in later cycles after delays and dose reductions. The incidence of grade 3 or 4 neuropathy was similar in patients with pre-existing grade 1 or 2 neuropathy (13 [13%] of 103 patients had grade 3; no grade 4) and in those without pre-existing neuropathy (grade 3: 27 [7%] of 386 patients; grade 4: two [1%] of 386 patients). Alopecia occurred in 224 (45%) of 503 patients on eribulin (grade 1: 132 [26%]; grade 2: 87 [17%]). Hypersensitivity related to the study drug occurred in four (1%) of 503 patients in the eribulin group and in one (<1%) of 247 patients in the TPC group.

An updated analysis of overall survival (not protocol prespecified) that was requested by European and US regulatory authorities included 589 deaths (386 [76%] in the eribulin group; 203 [80%] in the TPC group), compared with 422 in the primary analysis. These results confirmed the significant increase in overall survival for eribulin compared with TPC in the ITT population (HR 0·81; 95% CI 0·67–0·96; p=0·014; figure 5). Median overall survival was 13·2 months (95% CI 12·1–14·4) with eribulin and 10·5 months (9·2–12·0) with TPC; the 1-year survival rate was 54·5% with eribulin and 42·8% with TPC.

Comprehensive data for post-trial treatments were not required per protocol, apart from the first anticancer treatment after the study treatment for the purpose of censoring for progression-free survival. Further information was not requested. On the basis of the available data, no differences were noted between the treatment groups with respect to this first anticancer treatment: chemotherapy was received by 274 (54%) of 503 patients on eribulin and 123 (50%) of 247 patients on TPC; hormonal therapy by 52 (10%) patients on eribulin and 30 (12%) patients on TPC; and radiotherapy by 34 (7%) eribulin patients and eight (3%) TPC patients.

Discussion

This global phase 3 study establishes a potential new standard treatment for women with heavily pretreated metastatic breast cancer, for whom there was previously no chemotherapy treatment with proven survival benefit (table 4; panel). The study met its primary endpoint of significant improvement in overall survival with eribulin versus real-life treatment choices at the time (2006–08) for women with metastatic breast cancer who had received a median of four previous chemotherapy regimens. To our knowledge, EMBRACE is the first major single-agent study of a cytotoxic or biological agent to show significantly increased survival in patients with such heavily pretreated metastatic breast cancer. Importantly, these benefits are clinically meaningful,

because the 2·5-month extension of median survival represents an increase of 23% for these women, which is similar to that reported with docetaxel versus mitomycin plus vinblastine (31%)[23] and capecitabine plus docetaxel versus docetaxel (26%).[24] Finally, the benefits of eribulin were achieved with a manageable profile of toxic effects. On the basis of the results of this study, eribulin has received approval in the USA for patients who have received at least two chemotherapeutic regimens for the treatment of metastatic breast cancer, with previous treatment including an anthracycline and a taxane.

The secondary surrogate efficacy endpoints, objective response rate and progression-free survival, were consistent with the primary endpoint. Objective response rate was significantly improved with eribulin versus TPC, with a clinically meaningful median duration of response with eribulin of 4·2 months; duration of response seemed longer in the TPC group, but comparison between groups is inappropriate, because only ten patients responded to TPC. Progression-free survival was also longer with eribulin than with TPC, and was significant in the investigator review, but not the independent review; this apparent difference arose from the censoring of almost twice as many patients in the independent review than in the investigator review. Study scans stopped once the investigator had declared disease progression, leading to many censored patients in the independent review, who could only assess non-measurable disease for progression if non-target lesions progressed or new lesions appeared.

Subgroup analyses also supported the primary ITT population analysis. Eribulin clearly improved overall survival in region 1 compared with TPC; in regions 2 and 3, overall survival was similar with eribulin and TPC. These regions had, however, substantially smaller sample sizes than those of region 1, and recruitment started much later; CIs are, therefore, wide and overlapping, and results are less mature than for region 1. Likewise, for HER2 status and previous capecitabine treatment, and individual TPC agent, patient numbers were often small and CIs widely overlapping. An updated analysis of overall survival that was requested by European and US regulatory authorities confirmed the significant increase in overall survival for eribulin compared with TPC.

Eribulin had a manageable profile of toxic effects, which was consistent with earlier studies[10–14,25] and similar to those of other chemotherapeutic agents used in this setting. Eribulin also has a relative ease of administration, short infusion time, and no requirement for premedication to prevent hypersensitivity. Importantly, the overall incidence of serious adverse events and adverse events, adverse events leading to treatment delays or modification, and fatal adverse events were almost identical in the two groups. The most common grade 3 or 4 adverse event was neutropenia, but grade 3 or 4 febrile neutropenia was uncommon in both groups and the incidence of all treatment-related fatal adverse events was the same. Grade 3 or 4 asthenia or fatigue occurred with very similar frequency with eribulin and TPC. Peripheral neuropathy occurred in 174 (35%) of 503 patients with eribulin, but was grade 3 or 4 in only 41 (8%), and led to discontinuation in only 24 (5%) patients.

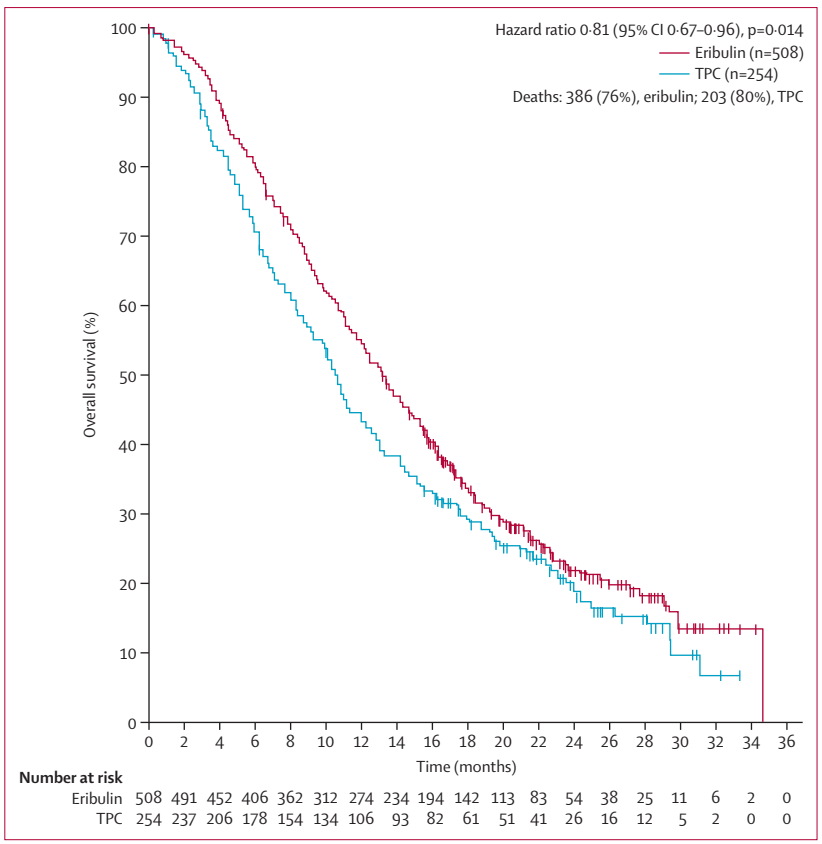

Figure 5: **Kaplan-Meier graph of overall survival in an updated analysis**
Analysis included the intention-to-treat population and was not protocol prespecified. Tickmarks show censored data. TPC=treatment of physician's choice.

This trial design had two features that might be viewed as potential weaknesses: the TPC control group and the primary endpoint of overall survival. TPC included several different chemotherapies, each with their own characteristic toxic effects, precluding detailed comparisons with eribulin. Likewise, the relief of symptoms associated with metastatic breast cancer is an important treatment goal, but the differing TPC agents would have complicated the interpretation of quality of life, therefore this analysis was not protocol prespecified and there are no data for inclusion in the paper. This absence of data is a limitation of the study, but is arguably less significant in the context of eribulin having extended overall survival. Quality of life is, however, being investigated in ongoing trials, including one comparing eribulin with capecitabine in women with pretreated metastatic breast cancer. Bias might have been introduced through best supportive care only being an option in the TPC group, but this effect was

	Primary endpoint	Patient population	Treatment groups	OS		PFS or TTP		ORR (%), p value
				Median (months)	HR (95% CI; p value)	Median (months)	HR (95% CI; p value)	
Single-agent studies								
EMBRACE study	OS	2–5 previous regimens (≥2 for locally recurrent or MBC)	Eribulin (n=508) *vs* TPC (n=254)	13·1 *vs* 10·6	0·81 (0·66–0·99; p=0·041)	3·7 *vs* 2·2 (PFS)	0·87 (0·71–1·05; p=0·137)	12% *vs* 5%, p=0·002
Barrios et al (2010)[17]	PFS	≤2 previous regimens (for MBC); no previous capecitabine	Sunitinib (n=238) *vs* capecitabine (n=244)	15·3 *vs* 24·6	1·17 (0·84–1·63; p=0·350)	2·8 *vs* 4·2 (PFS)	1·47 (1·16–1·87; p=0·999)*	11% *vs* 16%, p=0·109
Combination studies								
Miller et al (2005)[18]	PFS	1–2 previous regimens (for MBC)	Capecitabine plus bevacizumab (n=232) *vs* capecitabine (n=230)	15·1 *vs* 14·5	NR	4·9 *vs* 4·2 (PFS)	0·98 (0·77–1·25; p=0·857)	20% *vs* 9%, p=0·001
Geyer et al (2006)[19]	TTP	≥4 previous cycles of regimens including anthracycline and taxane (adjuvant or MBC setting); previous trastuzumab; HER2-positive disease	Lapatinib plus capecitabine (n=163) *vs* capecitabine (n=161)	NR	NR	8·4 *vs* 4·4 (TTP)	0·49 (0·34–0·71; p<0·001)	22% *vs* 14%, p=0·09
Thomas et al (2007)[20]	PFS	≤3 previous regimens (adjuvant or MBC setting)	Ixabepilone plus capecitabine (n=375) *vs* capecitabine (n=377)	NR	NR	5·8 *vs* 4·2 (PFS)	0·75 (0·64–0·88; p=0·0003)	35% *vs* 14%, p<0·0001
Sparano et al (2010)[21]	OS	≤2 previous regimens (adjuvant or MBC setting)	Ixabepilone plus capecitabine (n=609) *vs* capecitabine (n=612)	16·4 *vs* 15·6	0·90 (0·78–1·03; p=0·116)	6·2 *vs* 4·4 (PFS)	0·79 (0·69–0·90; p=0·0005)	43% *vs* 29%, p<0·0001

MBC=metastatic breast cancer. OS=overall survival. PFS=progression-free survival. TTP=time to progression. ORR=objective response rate. HR=hazard ratio. TPC=treatment of physician's choice. NR=not reported. HER2=human epidermal growth factor receptor 2. *One-sided p value reported because there was no statistical evidence to support the hypothesis that sunitinib improved PFS compared with capecitabine.

Table 4: **Review of phase 3 trials in patients with MBC previously treated with an anthracycline and a taxane, including results of the EMBRACE study**

Panel: Research in context

Systematic review

A literature review published in 2010 assessed phase 3 studies of systemic therapy in metastatic breast cancer.[16] We also did a PubMed literature search on Sept 23, 2010, using the terms "breast neoplasms [MeSH]", "clinical trial", "phase iii [Publication Type]", "anthracycline AND taxane" (no date restriction) to identify phase 3 studies in metastatic breast cancer pretreated with both an anthracycline and a taxane. This search yielded 25 reports, of which only five reported phase 3 studies in this specific setting (table 4).

Interpretation

For overall survival, rather than a surrogate marker of efficacy, to be the primary endpoint in metastatic breast cancer trials is rare. Often, investigators argue that the effect of study treatment on overall survival will be confounded by subsequent treatments and competing causes of death in the first-line or second-line settings and by the inherently poor prognosis of heavily pretreated disease. However, the reliability of response or progression-free survival as surrogate markers for survival in metastatic breast cancer remains unclear.[22] In a literature review,[16] only five of 76 major phase 3 studies of systemic therapy in metastatic breast cancer defined overall survival as their primary endpoint, and none met its primary endpoint; the 15 studies reporting improved overall survival all did so as a secondary endpoint, and not in heavily pretreated patients. From the literature search of phase 3 studies in metastatic breast cancer pretreated with both an anthracycline and a taxane, none were in such heavily pretreated patients as were included in EMBRACE (table 4). Only one study had overall survival as a primary endpoint, which was not met.[21] Our demonstration of improved overall survival as the primary endpoint in women with metastatic breast cancer treated with cytotoxic therapy seems unique, and challenges the idea that such an expectation is unreasonable. This disease stage could, indeed, be the optimum setting in which to identify new agents with clinically important activity.

avoided by selection of the TPC treatment before randomisation. We would contend that the use of TPC was an important strength, because our results reflect real-life choices made by oncologists and their patients. The benefits of eribulin are, therefore, arguably more likely to be generalisable to clinical practice than if the control treatment had been artificially constrained.

In conclusion, this randomised phase 3 trial showed that eribulin is safe and significantly improved overall survival in women with heavily pretreated metastatic breast cancer compared with available cytotoxic therapy. The benefit that eribulin has shown as a single agent in this setting suggests that this drug could become a new standard of care; further evaluation earlier in the natural history of breast cancer is warranted. These results show that cytotoxic agents directed at a well defined target remain worthy of evaluation. They also challenge existing assumptions in trial design and suggest that extension of overall survival is a realistic and achievable aim during assessment of new treatments in women with heavily pretreated metastatic breast cancer.

Contributors

All authors were involved in the writing of the manuscript and approved the final draft. JC, JO'S, DL, JLB, LTV, KP, PC, AM, VD, TD, VV, FC, HK, PB, JW, and CT were involved in data collection. JC, JO'S, JLB, LTV, CED, JW, and CT were involved in study design, data analysis, and interpretation. DL, PC, VD, SS, DM, and NM were also involved in data analysis and interpretation.

Conflicts of interest

JC has received consultancy fees from Roche and Eisai. JO'S received honorarium from an Eisai advisory board. JLB has received consultancy fees/honorarium from Eisai. LTV has received consultancy fees from Bristol-Myers Squibb, Bayer, and Eisai; as well as payment for lectures and a grant to her institution from Bristol-Myers Squibb. PC's institution received a grant from Eisai for clinical management. VD has received both a grant from Eisai and participated in an advisory board. FC has received consultancy fees

from Eisai. PB has a patient for whom reimbursement for additional costs was received. CED, SS, DM, NM, and JW are employees of Eisai. CT reports receiving travel support from Eisai; consultancy fees from AstraZeneca, Pfizer, and Eisai; payment for lectures from Cephalon, Eisai, and Roche; payment for developing educational presentations from Bridgehead/Healthcare and Roche; travel and accommodation from Roche; and other support from Boehringer-Ingelheim, Celgene/Gloucester, and Sanofi-Aventis. DL, KP, AM, TD, VV, and HK declare that they have no conflicts of interest.

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See **Online** for webappendix