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Original Research

Eribulin mesilate versus vinorelbine in women with locally recurrent or metastatic breast cancer: A randomised clinical trial

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KEYWORDS
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Tolerability;
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Abstract ***Introduction:*** The objective of this study was to evaluate the efficacy and safety of eribulin monotherapy, relative to vinorelbine, in Chinese women with locally recurrent/metastatic breast cancer (MBC).
Methods: This phase III open-label, randomised, parallel-group, multicentre clinical trial enrolled patients with locally recurrent or MBC who had had 2–5 prior chemotherapy regimens, including an anthracycline and taxane) from September 26, 2013, to May 19, 2015. Women were randomised 1:1 to receive eribulin (1.4 mg/m^2, intravenously, on day 1 and

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Eribulin

day 8) or vinorelbine (25 mg/m^2, intravenously, on day 1, day 8 and day 15) every 21 days. The primary end-point was progression-free survival (PFS). Secondary end-points included objective response rate (ORR), duration of response and overall survival (OS).

Results: Five hundred thirty women were randomised to receive eribulin (n = 264) or vinorelbine (n = 266). Improvement in PFS was observed with eribulin compared with vinorelbine (hazard ratio [HR]: 0.80, 95% confidence interval [CI]: 0.65–0.98, P = 0.036); median PFS was 2.8 months in both treatment arms. The median OS was 13.4 months with eribulin and 12.5 months with vinorelbine (HR: 1.03, 95% CI: 0.80–1.31, P = 0.838). The ORR was 30.7% (95% CI: 25.2%–36.6%) with eribulin and 16.9% (95% CI: 12.6%–22.0%) with vinorelbine (P < 0.001). Treatment-emergent adverse events leading to treatment discontinuation were less frequent with eribulin (7.2%) than with vinorelbine (14.0%).

Conclusions: Eribulin achieved statistically significantly superior PFS (and response rate) compared with vinorelbine in previously treated women with locally recurrent or MBC. Eribulin appeared to be better tolerated than vinorelbine, with no new safety signals observed.

Trial registration: National Institutes of Health ClinicalTrials.gov registry, NCT02225470. Registered 05 August 2014- Retrospectively registered. https://clinicaltrials.gov/ct2/show/NCT02225470?term=NCT02225470&rank=1.

1. Introduction

Metastatic breast cancer (MBC) treatment remains palliative rather than curative, aiming to prolong survival and enhance or maintain quality of life [1,2]. Cytotoxic chemotherapy remains important in patients who become resistant to endocrine therapy and is currently one of a few approved systemic options for patients with triple-negative breast cancer [3]. Guidelines generally recommend sequential cytotoxic monotherapy for MBC, but no specific sequence of cytotoxic therapies has been advocated [1,2]; therefore, the choice is often determined by perceived relative efficacy and tolerability, the patient's comorbidities, performance status, preferences and prior adjuvant therapy. The increased use of anthracyclines and taxanes in the neo-adjuvant setting makes treatment selection at recurrence more challenging, and cumulative toxicity can limit therapeutic choices in heavily pretreated patients [4,5]. There remains, therefore, an unmet need for effective, well-tolerated treatments for patients with pretreated MBC.

Eribulin is a non-taxane microtubule inhibitor with a novel and distinct mode of action compared with taxanes and vinca alkaloids, binding predominantly to a small number of high-affinity sites on the growing (plus) ends of microtubules [6,7]. Eribulin also has other non-cytotoxic effects, including vascular remodelling, reversal of the epithelial–mesenchymal transition, induction of differentiation and suppression of migration and invasion [8–10]. Clinically, the benefits of eribulin in women with locally recurrent or MBC pretreated or resistant to anthracyclines and taxanes were established by the pivotal EMBRACE study, where eribulin significantly prolonged overall survival (OS) compared with treatment of physician's choice (TPC; median: 13.1 months versus 10.6 months) [11]. Subsequently, in Study 301, in less heavily pretreated patients, median OS with eribulin was numerically longer compared with capecitabine [12]. This difference was not, however, significant (median OS was 15.9 and 14.5 months for eribulin and capecitabine, respectively; hazard ratio [HR]: 0.88; 95% confidence interval [CI]: 0.77–1.00; $P = 0.056$) [12]. In both EMBRACE and Study 301, adverse events (AEs) associated with eribulin were considered manageable [11,12], and a similar impact on quality of life was observed with eribulin compared with capecitabine in Study 301 [13].

Vinorelbine is a vinca alkaloid that interferes with microtubule assembly by a different mechanism to that of eribulin [14]. Most monotherapy vinorelbine studies in locally advanced/MBC were single-arm designs with few comparative trials [15]. Vinorelbine was considered superior to melphalan with respect to time to progression (12 versus 8 weeks, respectively; $P < 0.001$) and OS ($P = 0.034$) [16]. In patients previously treated with both an anthracycline and a taxane, vinorelbine has not been shown to be superior to other single-agent chemotherapy, although progression-free survival (PFS) was significantly prolonged by the addition of gemcitabine to single-agent vinorelbine (6.0 months and 4.0 months, respectively; $P = 0.003$) [15,17].

The present study is the first designed to evaluate the efficacy and safety of eribulin compared with vinorelbine as monotherapies for the treatment of locally recurrent or MBC in Chinese women.

2. Methods

2.1. Study design

This was an open-label, randomised, parallel, 2-arm, multicentre study of eribulin versus vinorelbine in women

with pretreated locally recurrent or MBC conducted across 35 centres in China. The study was approved by each institutional research ethics board and conducted in accordance with the Declaration of Helsinki, guidelines of the International Conference for Harmonisation/Good Clinical Practice and local ethical and legal requirements.

The trial was registered with the ClinicalTrials.gov registry (NCT02225470).

2.2. Patients

All patients provided written informed consent. Eligible patients were women aged 18–70 years with histologically or cytologically confirmed breast cancer and locally recurrent or metastatic disease. Patients had to have received 2–5 prior chemotherapeutic regimens, at least 2 of which were for locally recurrent or MBC treatment, including an anthracycline and a taxane. Patients had measurable disease according to the Response Evaluation Criteria In Solid Tumours, version 1.1 (RECIST v1.1) [18], with documented progression within 6 months of their most recent chemotherapy. Patients were not eligible if they had received vinorelbine as adjuvant or neo-adjuvant therapy within 1 year prior to the first treatment, or if progressive disease had occurred within 6 months after the last treatment of vinorelbine. Further details on eligibility criteria are in the Supplementary Methods.

2.3. Randomisation and masking

Patients were randomly assigned 1:1 to treatment with either eribulin or vinorelbine using an interactive web-response system. Randomisation was stratified according to receptor status (human epidermal growth factor receptor 2 [HER2] positive, HER2 negative but hormone receptor positive [non-triple negative], HER2 negative and hormone receptor negative [triple negative] or HER2 unknown), and the number of prior chemotherapy regimens (2–3 or 4–5). The sponsor did not have access to the aggregated efficacy summary data by treatment arm before database lock.

2.4. Procedures

Patients received 21-day cycles of either 1.4 mg/m^2 eribulin mesilate (equivalent to eribulin 1.23 mg/m^2 [expressed as free base]) intravenously over 2–5 min on days 1 and 8 of each cycle or 25 mg/m^2 vinorelbine intravenously on days 1, 8 and 15 of each cycle. Treatment continued until disease progression, unacceptable toxicity or withdrawal of consent. Tumour assessments per RECIST v1.1 (by independent radiologic review and by investigator) were performed at baseline, then every 6 weeks until disease progression or initiation of other anticancer therapy. Safety was monitored with AE reporting, regular clinical laboratory tests, physical examinations and electrocardiogram assessments.

2.5. Outcomes

The primary efficacy end-point was PFS by independent review, defined as the time between randomisation and the date of first documentation of disease progression or death from any cause, whichever occurred first. Secondary end-points included OS, objective response rate (ORR) and duration of response. Exploratory end-points included clinical benefit rate (CBR; defined as the proportion of patients with a complete response [CR], partial response [PR] or stable disease [SD] of $\geq$24 weeks' duration); disease control rate (DCR; defined as the proportion of patients who have best overall response of CR + PR + SD with duration of $\geq$12 weeks) and durable SD rate (defined as the proportion of patients who have a duration of SD $\geq$ 24 weeks). Relative dose intensity is defined as the actual dose intensity (mg/m^2/week)/planned dose intensity (mg/m^2/week).

2.6. Statistical analysis

The trial was powered to assess differences in PFS between the eribulin and vinorelbine groups. Assuming a median PFS of 2 months in the vinorelbine group, an HR of 0.75 for eribulin versus vinorelbine (based on a *post hoc* subgroup analysis of 61 patients treated with vinorelbine from the EMBRACE study [data on file]), an overall type I error rate of 2-sided 0.05 and the power of 80%, a total of approximately 380 progression events or deaths prior to disease progression were required for the primary analysis of PFS. The study initially planned to randomly assign 440 patients (n = 220 in each treatment arm), assuming 380 progression events would occur within 24 months with a 10% dropout rate. The proportion of censoring during the course of the study, according to independent review, was higher than expected; therefore, the sample size was increased to 530 patients (n = 265 in each treatment arm) to ensure the target number of 380 events would be reached in a reasonable time frame.

Primary efficacy analyses were performed on the intent-to-treat population. The data cutoff date for analyses was January 29, 2016. Median PFS and OS were estimated using the Kaplan–Meier method. The 2-sided 95% CIs of PFS and OS estimates were calculated with the Greenwood formula. Differences between the two groups for PFS were evaluated using the stratified log-rank test with receptor status and the number of prior chemotherapy regimens as strata. The HRs and 95% CIs were estimated using the Cox proportional hazard model with receptor status and the number of prior chemotherapy regimens as strata. Censoring rules for PFS followed the United States Food and Drug Administration guidance [19].

The safety analyses set comprised all randomised patients who received at least 1 dose of study treatment and had at least 1 postbaseline safety evaluation. AE severity was characterised according to the Common Terminology Criteria for Adverse Events, version 4.0. Statistical analyses were performed using SAS, version 9.4. Additional statistical methods are provided in the Supplementary Methods.

3. Results

Overall, 530 patients were enrolled between September 26, 2013, and May 19, 2015; 264 patients were randomised to eribulin and 266 to vinorelbine (Fig. 1). All patients in the eribulin group received treatment, but seven patients in the vinorelbine group did not receive treatment (withdrawal of consent, n = 6; other, n = 1). At the time of data cutoff (January 29, 2016), seven patients (2.7%) in the eribulin and two (0.8%) in the vinorelbine group remained on study treatment.

Baseline characteristics were balanced between groups (Table 1). All patients were women of Chinese ethnicity, with a mean age of 50.3 and 49.2 years in the eribulin and vinorelbine groups, respectively. Most women had invasive ductal carcinoma in both the eribulin and vinorelbine groups (87.1% and 85.3% of patients, respectively) and almost all had distant metastases (95.1% and 93.6%, respectively). Patients

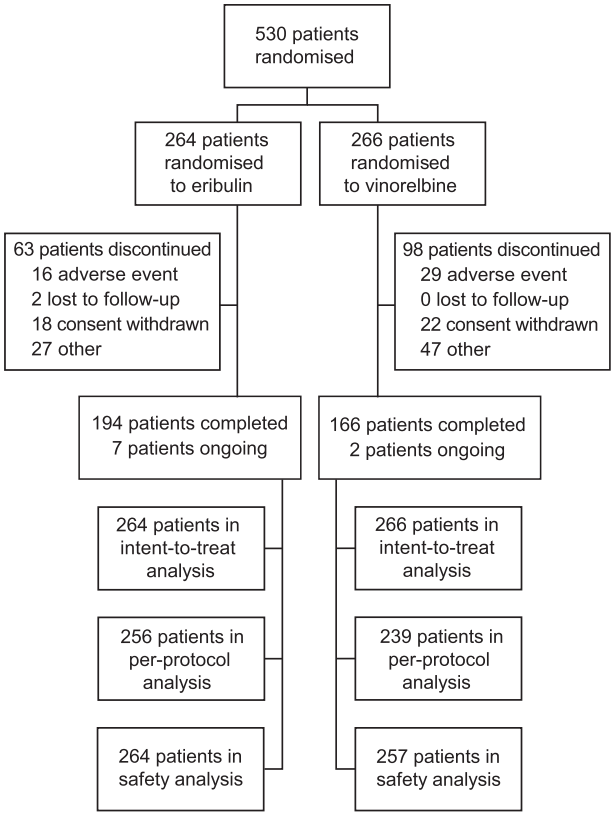


Fig. 1. Trial participant profile.

Table 1
Baseline demographic and clinical characteristics of the intent-to-treat population.

Characteristic	Eribulin (n = 264)	Vinorelbine (n = 266)
Age, mean years (standard deviation)	50.3 (9.8)	49.2 (9.6)
ECOG performance status		
0	57 (21.6)	52 (19.5)
1	196 (74.2)	205 (77.1)
2	11 (4.2)	9 (3.4)
Years since diagnosis		
0 to <2	43 (16.3)	43 (16.2)
2 to <10	194 (73.5)	187 (70.3)
≥10	27 (10.2)	36 (13.5)
Histological type		
Non-invasive ductal carcinoma	2 (0.8)	3 (1.1)
Invasive ductal carcinoma	230 (87.1)	227 (85.3)
Other invasive carcinoma[a]	28 (10.6)	31 (11.7)
Missing	4 (1.5)	5 (1.9)
Metastases		
Yes	251 (95.1)	249 (93.6)
No	13 (4.9)	17 (6.4)
HER2 receptor status[b]		
Positive	52 (19.7)	52 (19.5)
Negative	200 (75.8)	199 (74.8)
Unknown	12 (4.5)	15 (5.6)
ER status		
ER positive	148 (56.1)	151 (56.8)
ER negative	109 (41.3)	111 (41.7)
ER unknown	7 (2.7)	4 (1.5)
PR status		
PR positive	117 (44.3)	135 (50.8)
PR negative	140 (53.0)	127 (47.7)
PR unknown	7 (2.7)	4 (1.5)
HR status		
HR positive	160 (61)	165 (62)
HR negative	97 (36.7)	97 (36.5)
HR unknown	7 (2.7)	4 (1.5)
Triple (HER2/ER/PR) negative	64 (24.2)	68 (25.6)
Number of prior chemotherapy regimens		
2	25 (9.5)	13 (4.9)
3	109 (41.3)	121 (45.5)
4	73 (27.7)	81 (30.5)
5	49 (18.6)	50 (18.8)
≥6	8 (3.0)	1 (0.4)
Prior therapies		
Refractory to taxanes	119 (45.1)	146 (54.9)
Refractory to anthracyclines	46 (17.4)	44 (16.5)
Any vinorelbine	43 (16.3)	41 (15.4)
Any HER2-targeted therapy	14 (5.3)	21 (7.9)
Any hormonal therapy	153 (58.0)	155 (58.3)
Any surgery	244 (92.4)	249 (93.6)
Any radiotherapy	179 (67.8)	168 (63.2)

ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; FISH, fluorescent in situ hybridisation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; PR, progesterone receptor.
All patients were women of Chinese ethnicity. Data are n (%), except where noted.
[a] Includes six missing in the eribulin group and nine missing in the vinorelbine group.
[b] Based on the American Society of Clinical Oncology/College of American Pathologists guideline recommendations, HER2 status was programmatically derived from case report form data as follows: If FISH present then HER2 = classification by FISH; if FISH not done and IHC = −, + or ++, then HER2 = negative; if FISH not done and IHC = +++, then HER2 = positive; otherwise, HER2 = unknown.

received a median (interquartile range) of five cycles (3–8) and four cycles (2–6) of eribulin and vinorelbine, respectively. The median relative dose intensity was 0.83 for eribulin and 0.66 for vinorelbine.

In the ITT population, by independent review, a statistically significant improvement in PFS for eribulin was demonstrated compared with vinorelbine (HR: 0.80, 95% CI: 0.65–0.98, $P = 0.036$) (Fig. 2A). Median PFS was 2.8 months (95% CI: 2.8–4.1) for eribulin and 2.8 months (95% CI: 2.7–2.8) for vinorelbine. Consistent results were obtained in the per-protocol analysis (Fig. 2B), as well as by investigator assessments in both the ITT (Fig. 2C) and per-protocol (Fig. 2D) populations.

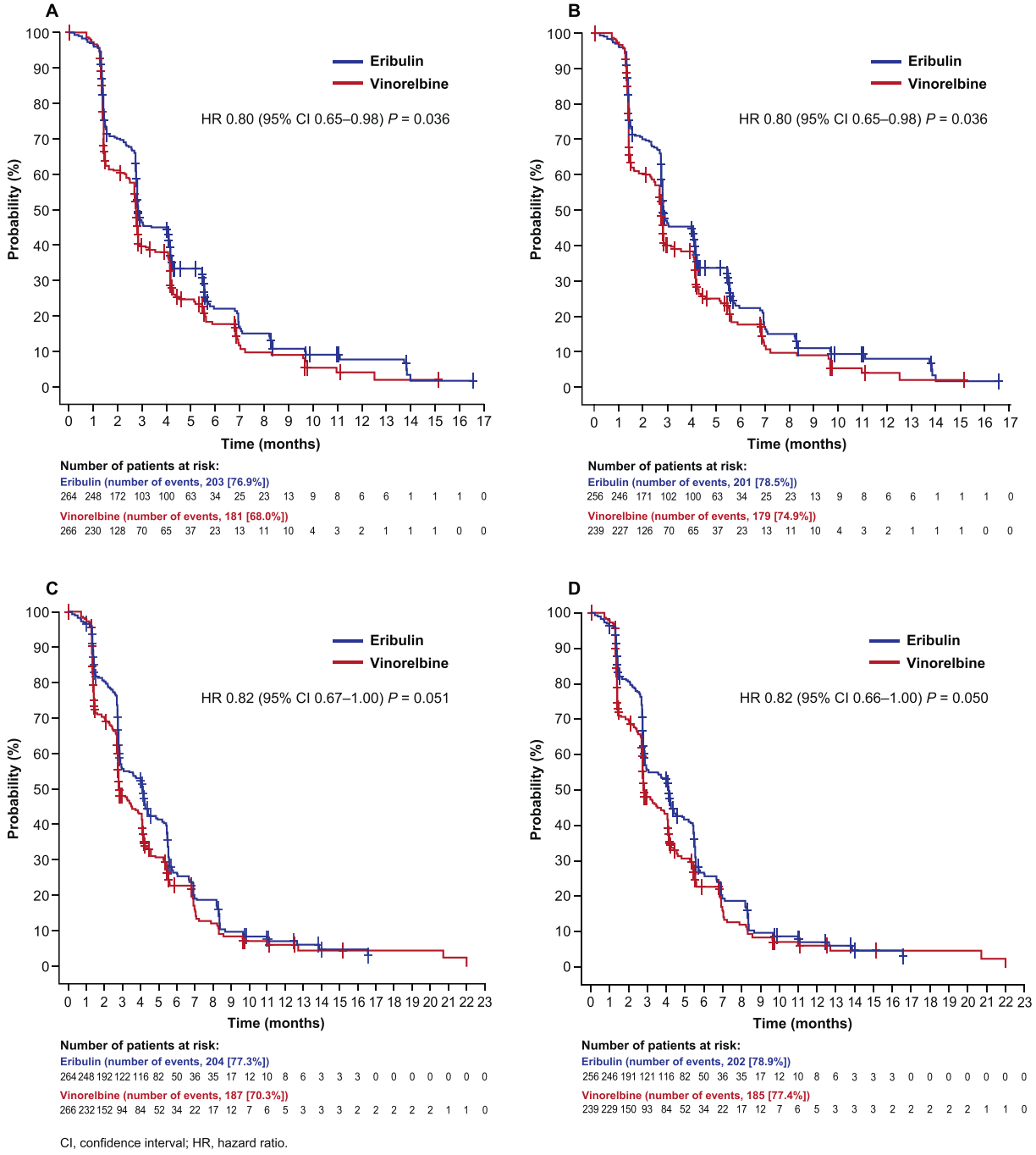
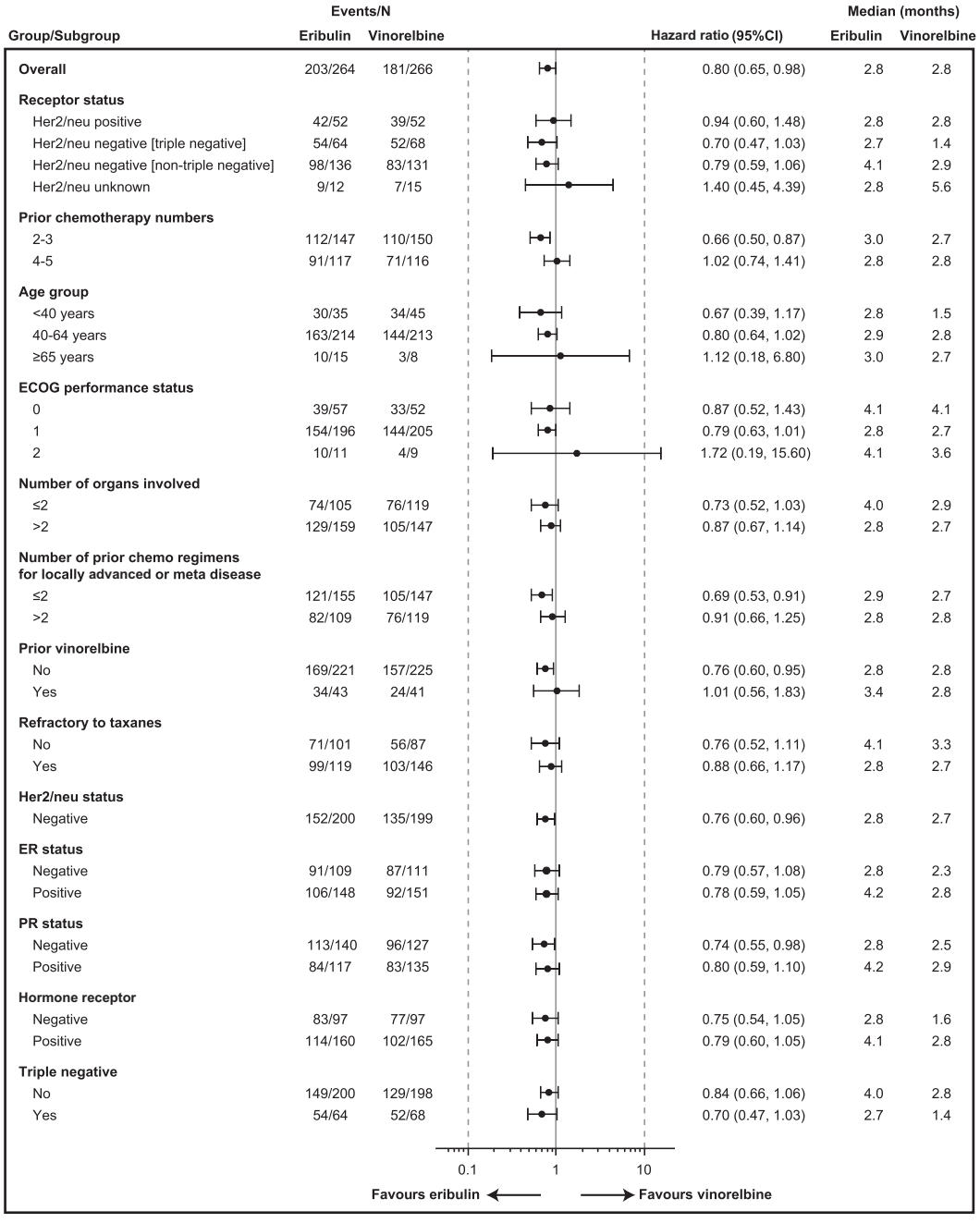


Fig. 2. Progression-free survival in patients treated with eribulin or vinorelbine according to *independent review* in the intent-to-treat population (A) or in the per-protocol population (B); or according to *investigator assessment* in the intent-to-treat population (C) or in the per-protocol population (D). HR, hazard ratio; CI, confidence interval.

The favourable impact of eribulin on PFS was supported by a *post hoc* sensitivity analysis, where the PFS time ratio of eribulin to vinorelbine was 1.19 (95% CI: 1.03–1.37, $P = 0.020$) (Additional Fig. 1). Additionally, in most subgroups, PFS was favoured with eribulin over vinorelbine, including in patients with HER2-negative disease (HR: 0.76, 95% CI: 0.60–0.96) and triple-negative disease (HR: 0.70, 95% CI 0.47–1.03) (Fig. 3).

The median OS for eribulin was 13.4 months (95% CI: 11.5–16.2) versus 12.5 months (95% CI: 10.6–16.6) with vinorelbine (HR: 1.03; 95% CI: 0.80–1.31, $P = 0.838$) (Additional Fig. 2A). The ORR for eribulin was 30.7% (95% CI: 25.2%–36.6%) compared with 16.9% (95% CI: 12.6%–22.0%) for vinorelbine ($P < 0.001$; Additional Fig. 2B). Additional Fig. 3 shows the maximum tumour changes in target lesions. In all



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; Her2, human epidermal growth factor receptor 2; HR, hormone receptor; PR, progesterone receptor; ORR, overall response rate.

Fig. 3. Forest plot of hazard ratio in progression-free survival, Independent review, intent-to-treat population. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PR, progesterone receptor; ORR, overall response rate.

subgroups examined, ORR numerically favoured eribulin, including in patients with HER2-negative disease (odds ratio: 1.92, 95% CI: 1.20–3.06) and patients who had received 4–5 prior chemotherapy regimens (odds ratio 3.20, 95% CI: 1.60–6.44) (Additional Fig. 4).

Grade 3 or higher treatment-emergent adverse events (TEAEs) occurred in 90.2% of eribulin-treated patients and in 88.3% of vinorelbine-treated patients and were generally similar between groups, except for ≥ grade 3 anaemia, which occurred more frequently in the vinorelbine group (18.3%) than the eribulin group (2.3%) (Table 2). Alopecia (all grades) occurred in 10 patients (3.8%) in the eribulin group and no patients (0%) in the vinorelbine group. Peripheral neuropathy (all grades) occurred in 2 (0.8%) patients in each treatment group. Febrile neutropenia ≥grade 3 occurred in seven patients in the eribulin arm (2.7%) and three in the vinorelbine arm (1.2%). There were no instances of ≥grade 3 neuropathy peripheral in the eribulin group compared with one occurrence in the vinorelbine group; similarly, there were no patients with ≥grade 3 peripheral sensory neuropathy in the eribulin group compared with one patient in the vinorelbine group. Treatment-related serious AEs occurred in 6.1% of eribulin-treated patients and 7.8% of vinorelbine-treated patients. A total of 10 patients died from TEAEs: six in the eribulin arm and four in the vinorelbine arm. Of these fatal events, two (neutrophil count decreased and capillary leak syndrome) in the eribulin arm and one (hepatic function abnormal) in the vinorelbine arm were considered treatment related.

TEAEs leading to treatment discontinuation were less frequent in patients receiving eribulin (19 patients [7.2%]) than vinorelbine (36 patients [14.0%]). Dosing modifications owing to TEAEs were less frequent in the eribulin group than the vinorelbine group, including dose reductions (14.8% versus 50.6%), missed doses (13.3% versus 79.8%) and missed or delayed doses (56.8 versus 79.8%).

4. Discussion

This randomised, multicentre, phase III study achieved its primary end-point, with statistically significantly longer PFS in patients randomised to eribulin versus vinorelbine (HR: 0.80, 95% CI: 0.65–0.98, $P = 0.036$) in Chinese women with previously treated locally recurrent/MBC. Eribulin was also better tolerated than vinorelbine, with fewer TEAEs leading to treatment discontinuation (7.2% and 14.0%, respectively). This study is the first to evaluate the efficacy and safety of eribulin in Chinese women. Our results indicate that the efficacy of eribulin in a Chinese population was similar to that reported in previous phase III trials [11,12] and that toxicity profiles for both vinorelbine and eribulin were as expected, with no new safety signals observed.

Although the HR of 0.8 for PFS indicated a 20% risk reduction in progression events with eribulin overall, the median PFS was 2.8 months in both study arms. This can be explained by the nature of the statistical analyses and visual inspection of the data. Percentiles (e.g. median) as a point measurement may occasionally be unstable

Table 2
Treatment-emergent adverse events occurring in 10% or more of patients, in either arm.

System organ class preferred term, n (%)	Eribulin (n = 264)		Vinorelbine (n = 257)	
	All Grades	≥Grade 3	All Grades	≥Grade 3
Investigations				
White blood cell count decreased	245 (92.8)	170 (64.4)	235 (91.4)	179 (69.6)
Neutrophil count decreased	237 (89.8)	211 (79.9)	230 (89.5)	198 (77.0)
Aspartate aminotransferase increased	110 (41.7)	4 (1.5)	71 (27.6)	3 (1.2)
Alanine aminotransferase increased	93 (35.2)	4 (1.5)	63 (24.5)	1 (0.4)
Haemoglobin decreased	59 (22.3)	6 (2.3)	73 (28.4)	10 (3.9)
Platelet count decreased	51 (19.3)	8 (3.0)	45 (17.5)	9 (3.5)
Blood glucose increased	28 (10.6)	3 (1.1)	23 (8.9)	4 (1.6)
Granulocyte count decreased	27 (10.2)	24 (9.1)	23 (8.9)	18 (7.0)
Metabolism and nutrition disorders				
Decreased appetite	30 (11.4)	1 (0.4)	34 (13.2)	2 (0.8)
Hypokalaemia	27 (10.2)	5 (1.9)	12 (4.7)	3 (1.2)
General disorders and administration site conditions				
Asthenia	63 (23.9)	5 (1.9)	81 (31.5)	10 (3.9)
Pyrexia	61 (23.1)	4 (1.5)	49 (19.1)	4 (1.6)
Gastrointestinal disorders				
Nausea	32 (12.1)	0	40 (15.6)	1 (0.4)
Vomiting	35 (13.3)	1 (0.4)	29 (11.3)	2 (0.8)
Constipation	32 (12.1)	0	44 (17.1)	3 (1.2)
Blood and lymphatic system disorders				
Anaemia	77 (29.2)	6 (2.3)	112 (43.6)	47 (18.3)

Treatment-related fatal (grade 5) adverse events in the eribulin group: neutrophil count decreased (n = 1) and capillary leak syndrome (n = 1); in the vinorelbine group: hepatic function abnormal (n = 1).

estimates because they are heavily dependent on the local shape of the Kaplan–Meier curve; thus, they may not be representative of the entire curve. The Kaplan–Meier PFS curves, from which the statistically significant improvement in PFS is derived, reflect the full course of treatment up to a progression event. At the first assessment point, after two cycles, substantially fewer women in the eribulin arm came off study because of disease progression in the eribulin arm than in the vinorelbine arm (n = 37 and n = 56, respectively; data not shown). This may reflect greater efficacy of eribulin in women with more aggressive disease because this separation was maintained step-wise at each assessment point, consistently favouring eribulin. However, the point at which median progression was assessed coincided with one of the occasions when the curves briefly came together. That this apparent discordance between the HR for PFS and median PFS estimates can be considered spurious is supported by the exploratory analysis of restricted mean PFS, which favoured eribulin over vinorelbine (4.4 months and 3.7 months, respectively). This interpretation is further supported by a sensitivity analysis in which the PFS time ratio significantly favoured eribulin (1.19, $P = 0.020$) and by subgroup analyses of PFS, most of which favoured patients randomised to eribulin. Finally, eribulin also significantly improved ORR, CBR and DCR compared with vinorelbine; OS appeared comparable with vinorelbine and was not statistically significant (13.4 versus 12.5 months, $P = 0.838$), but it should be noted that this study was not powered to detect a difference in OS between arms.

Vinorelbine was the most frequent TPC in the control arm of the EMBRACE study–administered to 25% of patients [11]. Of note, both PFS and OS in the vinorelbine arm of the current study (2.8 and 12.5 months, respectively) were comparable with PFS and OS in the control arm of the EMBRACE study (2.2 and 10.6 months, respectively) [11]. Finally, in this current study, prior treatment with vinorelbine, which was allowed under specific circumstances, was administered to similar proportions of patients in the eribulin and vinorelbine arms (16.3% and 15.4%, respectively). Therefore, the vinorelbine regimen used in the current trial represents a reasonable comparator arm.

We also note that in this study, although nearly 20% of patients had HER2-positive disease, only 5.3% and 7.9% of patients in the eribulin and vinorelbine arms, respectively, had received prior HER2-targeted therapy. A likely explanation for the low proportion of patients who received targeted therapy is limited patient access. For example, although trastuzumab was approved in China in 2002, it is often not included in reimbursement listings, and its high out-of-pocket costs render treatment unattainable for many patients in China [20,21].

One limitation of the current study is the lack of quality-of-life or patient-reported outcome measures. However, in the current study, both eribulin and vinorelbine were generally well tolerated. Peripheral neuropathy was very uncommon in both treatment arms (0.8% in each arm), and no peripheral neuropathy of ≥grade 3 was observed in the eribulin arm. Interestingly, despite apparently similar TEAE profiles, eribulin seemed to have better overall tolerability than vinorelbine, as evidenced by the substantially lower incidence of TEAE-related treatment discontinuations and dose reductions, interruptions or delays.

5. Conclusions

In summary, this study provides valuable comparative data for eribulin and vinorelbine, two monotherapy agents recommended for use in women with locally advanced or MBC. The primary end-point of achieving a statistically significant improvement in PFS for women treated with eribulin compared with vinorelbine was achieved. This translated to a modest improvement in mean (but not median) PFS, providing further evidence of the efficacy of eribulin in women with previously treated locally recurrent or MBC. To our knowledge, this is the second study (after EMBRACE [11]) in women with locally recurrent or MBC where eribulin has shown a statistically significant improvement in the primary efficacy outcome measure. Taken with evidence of reduced toxicity, the current study supports the use of eribulin in women with recurrent/MBC who have previously received an anthracycline and a taxane.

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Conflict of interest statement

P.Y., X.H., T.S., W.L., Q.Z., S.C., Y.C., Q.O., X.W., Z.C. and B.X. declare no competing interests. M.H., K.S. and S.F. are employees of Eisai Co., Ltd., Japan.

Data access, responsibility and accuracy

All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Presentations of the work in abstract form

Xu B, Sun T, Yuan P *et al.*: An Open-label, Randomized, Parallel, Two-arm, Multicenter Study of Eribulin

(ERI) Versus Vinorelbine (VNR) in Female Subjects With Locally Recurrent or Metastatic Breast Cancer (MBC). Orally presented at the Chinese Society for Clinical Oncology; Xiamen, China; 21–25 Sep 2016.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.02.002.

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