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Oncology

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Research Article
Eribulin treatment for patients with metastatic breast cancer: The United Kingdom experience—a multicenter retrospective study

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Short Title (max 80 characters; no abbrevs):
Eribulin for metastatic breast cancer: real-world data

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Abstract 199/300 max

Introduction: This study examined real-world data from patients who received eribulin for metastatic breast cancer (MBC) collected from 14 hospitals across the UK.

Methods: Anonymized data were collected retrospectively from patients with MBC who had received eribulin. The data included hormone-receptor status, histological diagnosis, age, prior chemotherapy, response to eribulin, progression-free survival (PFS), and overall survival (OS).

Results: Among 577 patients analyzed, the median age was 56 years and most patients (73%) were estrogen-receptor positive. The median OS was 288 days (95% confidence interval [CI]: 261–315) and the PFS was 117 days (95% CI: 105–129). Median OS was higher among older patients (≥ 65 vs < 65 years: 325 days [95% CI: 264–385] vs 285 days [95% CI: 252–317]; P = 0.028). Median OS was also higher in patients that received eribulin after fewer prior lines of chemotherapy (≤ 2 vs > 2 prior: 328 days [95% CI: 264–385] vs 264 days [95% CI: 229–298]; P = 0.042).

Discussion/Conclusion: These retrospective data suggest eribulin can be successfully used in older patients with MBC. Eribulin treatment was more effective in earlier-line settings which, while predictable, supports consideration of eribulin as a second-line treatment option.

Background

Metastatic breast cancer (MBC) is considered fairly common, since 5–10% of patients with breast cancer present with de novo metastatic disease at diagnosis and an additional 30% of breast cancer patients later develop metastases [1, 2]. Although there has been progress in the treatment of breast cancer, MBC remains a leading cause of cancer death for women worldwide. The median survival time ranges from 8–18 months for patients with triple-negative MBC [3, 4], and 3–5 years for those with hormone-receptor positive MBC [4, 5]. Management is challenging as the heterogenous nature of MBC results in varying clinical outcomes and responses to therapy [6]. Unfortunately, deciding on an appropriate therapeutic sequence to treat MBC using evidence-based medicine results is difficult because many studies do not track post-progression treatment and response [6].

Eribulin is approved in the United Kingdom (UK) for the treatment of patients with locally advanced or MBC based on the results of 2 pivotal studies, EMBRACE and Study 301 [7, 8]. Eribulin is recommended for patients who have progressed after ≥ 1 line of chemotherapy for advanced disease, which should have included an anthracycline and a taxane [9]. The mechanisms of action for eribulin have been previously published [10-12]. Briefly, eribulin is a synthetic analogue of halichondrin B and inhibits the growth phase of microtubules without inhibiting the shortening phase [13]. In the clinical setting, eribulin has been evaluated in heavily pretreated patients with MBC. In EMBRACE, patients had received two to five lines of prior chemotherapy [7] and in Study 301, patients had up to three lines of treatment [8]. In EMBRACE, eribulin was compared with physician's choice and was associated with an improved overall survival (OS) of 13.1 months (95% CI: 11.8–14.3) compared with 10.6 months (95% CI: 9.3–12.5; P = 0.041) [7]. Eribulin was not shown to be superior to capecitabine in Study 301 [8] but it was superior to vinorelbine in terms of PFS and ORR in Chinese women with pretreated MBC [14]. Although eribulin has shown promise as a treatment for patients with heavily pretreated MBC, its effects on patients in earlier stages of treatment is unknown. Since the patient populations in clinical trials (which must meet exact inclusion and exclusion criteria) are not entirely generalizable to the total population of patients with MBC [15-17], evaluation of eribulin in real-world settings is warranted.

There are few evaluations of eribulin in real-world settings, and most have focused on patients with heavily pretreated MBC [15-20]. However, there are some data to support eribulin use in an earlier-line setting. A recent real-world study investigating the impact of eribulin on survival in patients with MBC found that patients with zero or one prior line(s) of therapy had improved OS (median 555 days; 95% CI: 475–568) compared with patients with three or more prior lines of therapy (median 383 days; 95% CI: 342–459) [21]. A study comparing the efficacy of eribulin for Taiwanese women with MBC found a trend towards an increase in the objective response rate in patients with fewer prior lines of treatment; although, the difference was not significant [17].

The Cancer Drugs Fund in the UK was established in 2010 to aid in increasing access to cancer drugs that had not been or were in the process of being appraised by the National Health Service [22]. Eribulin was made available to patients via the Cancer Drugs Fund if they received at least two prior lines of treatment. Patients who were human epidermal growth factor receptor 2 (Her2) negative and had previously received at least one line of treatment for advanced disease could also qualify to receive eribulin through the Cancer Drugs Fund [23]. Most patients who have received eribulin in the UK thus far have received it after ≥ 2 lines of treatment. Here, we describe the demographics and survival profiles of patients who received eribulin for MBC in the UK using data from several different institutions treating a diverse population.

Methods

Study Design

This real-world study analyzed data from patients with MBC who had been treated with eribulin and was collected from 14 hospitals across the UK. The data were retrospective and obtained using computer and chemotherapy records. Data were collected on the initial histological diagnosis including histological subtype, tumor grade, receptor status (estrogen receptor [ER] and Her2), age, previous chemotherapy, response to eribulin, adverse events, OS, and progression-free survival (PFS). Adverse events were summarized as the presence or absence of nausea (any-grade severity), or severe (grade 3–4) neutropenia and neuropathy.

The data-collection plans received individual trust review board approval as audits of clinical services. Data were analyzed anonymously and, therefore, informed consent was not required.

Statistical Methods

OS and PFS were estimated using the Kaplan–Meier method. Significant differences and *P* values were calculated based on a Mantel–Cox log-rank test. Evaluations were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA).

Results

Patient Demographics

Data were collected from 592 patients who received eribulin in specialist cancer centers, teaching hospitals, and cancer units throughout the UK between 2011 and 2017. Pharmacy records were used to identify and select patients that received a previous line of treatment. Patient age distribution in the intent-to-treat (ITT) population is presented in Figure 1A. The efficacy analysis set consisted of the data collected from 577 patients who received at least one complete cycle of eribulin. The median age of patients was 56 years old (range, 33–84 years). Multiple types of MBC were represented: 129 patients had triple-negative MBC (22%); 419 (73%) were ER-positive, and 158 (27%) were ER-negative (Fig. 1B); 100 (17%) patients were Her2-positive, 475 (82%) were Her2-negative, and one patient had an unknown Her2 status (Fig. 1C). The majority of patients (80%) had ductal carcinoma of no special type.

Burden of disease

Patients had numerous sites of metastases, and some patients had multiple sites of metastases (Fig. 2A). Bone metastases were present in 351 patients (60.8%), lymph node metastases in 303 patients (52.5%), liver metastases in 262 patients (45.4%), and brain metastases in 65 patients (11.3%; Fig. 2A).

Prior treatments

Patients had a median of 3 (range, 1–10) different types of chemotherapy treatments prior to receiving eribulin (Fig. 2B). The majority of patients had received prior taxanes (91%) and capecitabine (82%). The median number of eribulin cycles received by patients was 5 (range, 1–29). Data on initial eribulin dosing was available for 209 patients (36.2%): the full, licensed, dose was given to 165 patients (78.9%), while an 80% dose was given to 36 patients (17.2%), and a 50% dose was given to 8 patients (3.8%). Of the patients for whom dosage information was available, 57 (27.3%) required a dose reduction during treatment with eribulin.

Efficacy

The median OS was estimated to be 288 days (95% CI: 261–315 days) and the median PFS was 117 days (95% CI: 105–129). Patients with triple-negative disease had worse OS and PFS compared with patients with other disease types. The median OS for patients with triple-negative disease was 234 days (95% CI: 263–293), while the remainder of the MBC patient cohort had a median OS of 308 days (95% CI: 279–338; *P* = 0.025; Fig. 3). The median PFS for patients with triple-negative disease was 89 days (95% CI: 71.6–106.4), while the remaining patients had a median PFS of 132 days (95% CI: 116.1–147.9).

Burden of disease

There was no significant difference in the OS or PFS of patients with liver or lung metastases. Patients with liver metastases had an OS of 299 days (95% CI: 259–339) and patients with lung metastases had an OS of 279 days (95% CI: 242–316). Patients with a brain metastasis had a decreased OS (221 days; 95% CI: 167–274) as compared with those without (279 days; 95% CI: 243–314; *P* = 0.06; Fig. 4).

Prior lines of chemotherapy

The median OS for patients receiving eribulin after ≤ 2 prior lines of chemotherapy was 328 days (95% CI: 264–385) compared with 264 days (95% CI: 229–298; *P* = 0.042; Fig. 5) for those who received > 2 prior lines of chemotherapy.

Age

The median OS in the ITT population for patients ≥ 65 years old was 325 days (95% CI: 264–385) compared with 285 days (95% CI: 252–317; *P* = 0.028) for those who were < 65 years old (Fig. 6).

Safety/tolerability

The data reported that neuropathy events of grade 3–4 severity occurred in 11% of patients. Nausea (all grades) was experienced by 14% of patients, and neutropenia of grade 3–4 severity was reported for 19% of patients. No patients in this study were recorded as having a treatment-related death.

Discussion/Conclusion

This real-world data analysis, gathered from hospitals throughout the breadth of the UK, supports the use of eribulin as a second-line treatment in MBC. OS was improved when eribulin treatment was given at an earlier line (after ≤ 2 prior lines of chemotherapy) compared with a subsequent line. When administered to an unselected population, eribulin was associated with an OS approaching 1 year.

These data are a more representative sample of the general population than clinical trial data. Patients receiving treatment for MBC in the real-world tend to be frailer (i.e., with more advanced disease or additional co-morbidities) than those in the clinical trial setting [24, 25]. Both EMBRACE and Study 301 had inclusion criteria that required an Eastern Cooperative Oncology Group performance status of 0–2 and adequate liver function as evidenced by bilirubin levels ≤ 1.5 times the upper limits of normal (ULN) and alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase levels ≤ 3 x ULN (in the case of liver metastases, ≤ 5 x ULN) [7, 8]. In this analysis, patients were also included from a wide range of hospitals, including specialized cancer centers in large cities, urban cancer units, and rural cancer units, which are not always encompassed in clinical trials.

The data are more generalizable and provide real-world expectations of outcomes for patients considering treatment with eribulin in the UK. The rationale was similar for other real-world studies related to eribulin treatment outcomes in India [15], Taiwan [17], and France [20]. Another important finding was that older patients (≥ 65 years old) had improved OS compared with those who were younger. Patients in EMBRACE had a median age of 55 years old (range, 27–85), and only 19.8% of patients were aged 65 years or older. This real-world study had a patient population with a median age of 56 years and a greater representation of older patients (≥ 65 years old; 24%; n = 141/591). Prior investigations support the safety and efficacy of eribulin for older patients in a real-world setting [16, 26], and taken together, our data reassure that eribulin can be used successfully in older adult patients with MBC. This is an important consideration given that patients with breast cancer tend to be diagnosed at an older age, and currently there is an increase in older patients with metastatic disease for whom evidence-based data is limited.

In a pooled post hoc analysis of EMBRACE and Study 301, eribulin nominally significantly improved OS versus the control treatment in patients with the following baseline metastases: bone, lymph node, liver and chest wall/breast/skin [27]. In our study, patients with liver or lung metastases had similar OS and PFS. However, we did note worse outcomes for patients with MBC and brain metastases compared to those without brain metastases; similarly, worse outcomes were observed among patients with triple-negative disease compared to patients who had Her2/ER-positive disease. Notably, brain metastases and triple-negative disease are both generally associated with poorer patient outcomes. The data showed that patients with brain metastases had numerically reduced survival compared with patients with liver and/or lung metastases. The better survival outcomes for patients with liver and/or lung metastases may represent a broader improvement in these aspects of the multidisciplinary management of breast cancer. We also observed longer survival outcomes for patients treated with eribulin in the second-line compared with later-line settings. These results are consistent with a previous study showing improvement in OS when eribulin was prescribed in patients who received fewer lines of treatment compared to control (capecitabine or treatment of physician's choice) [28].

There are limitations to comparing real-world data with clinical trials. Response Criteria In Solid Tumors (RECIST) are not routinely used to assess tumors in the real-world clinical setting. Assessments are based on radiological assessments of response or progressive disease, and different criteria may be used by different clinicians. While there remains an ongoing need to improve outcomes in patients with MBC, our data support the use of eribulin as a second-line treatment for MBC.

Statements
Statement of Ethics
The data-collection plans received individual trust review board approval as audits of clinical services. This study involved collection and analysis of anonymized data only, and, as such, it did not require any compliance with the Declaration of Helsinki. No ethics approval was needed for this research because this was a real-world/retrospective study using only anonymized data. No patients were directly involved.

Consent for publication
No identifiable individual patient data are contained in this publication; therefore, no permission was needed.

Author contributions:
Study concepts: Mariam Jafri.
Study design: Mariam Jafri.
Data acquisition: Mariam Jafri.
Quality control of data and algorithms: Mariam Jafri.
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Data availability

The source data used in this analysis will not be made publicly available; however, the authors may consider sharing this information on a case-by-case basis to individual researchers upon request. Further enquiries can be directed to the corresponding author.

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Figure Legends

Fig. 1. The age distribution in the ITT population (A), the ER status (B), and the Her2 status (C) of the eribulin-treated patient cohort.

ER, estrogen receptor; ITT, intent-to-treat; Her2, human epidermal growth factor receptor 2.

Fig. 2. The sites of metastases (A) and the number of prior lines of chemotherapy (B) among the patient cohort[a].

[a]Some patients may have had more than 1 site of metastasis.

Fig. 3. The Kaplan–Meier estimate of OS for patients with triple-negative MBC compared with patients with Her2/ER-positive MBC.

"Her2/ER-positive" were those patients who were ER-positive and/or Her2-positive.

ER, estrogen receptor; Her2, human epidermal growth factor receptor 2, MBC, metastatic breast cancer; OS, overall survival.

Fig. 4. The Kaplan–Meier estimate of OS for patients with or without brain metastases.
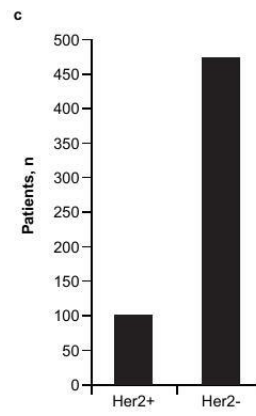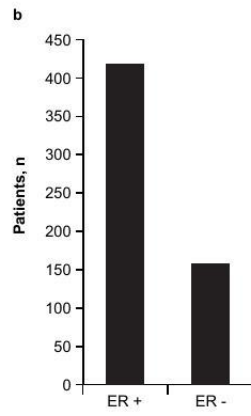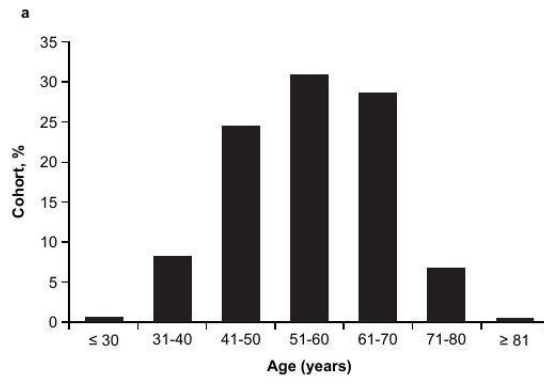
OS, overall survival.

Fig. 5. Kaplan–Meier estimate of OS for patients who had received > 2 lines of chemotherapy and for patients who had received ≤ 2 lines of chemotherapy before eribulin treatment (ITT population).
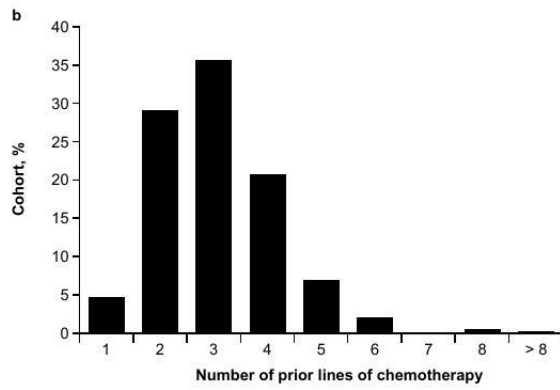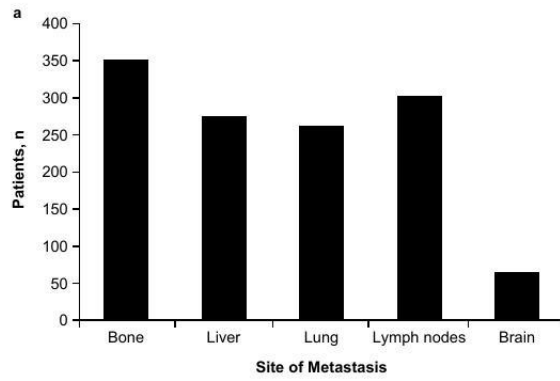
ITT, intent-to-treat; OS, overall survival.

Fig. 6. Kaplan–Meier estimate of OS for patients ≥ 65 years old compared with patients < 65 years old (ITT population).

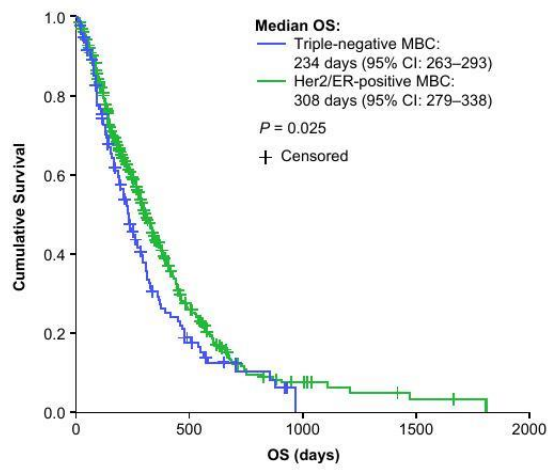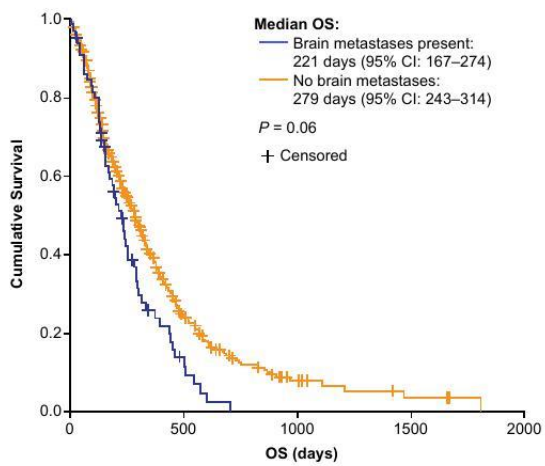ITT, intent-to-treat; OS, overall survival.

a

Cohort, % (y-axis, 0–35)

Age (years): ≤ 30, 31-40, 41-50, 51-60, 61-70, 71-80, ≥ 81

b

Patients, n (y-axis, 0–450)

ER +, ER -

c

Patients, n (y-axis, 0–500)

Her2+, Her2-

a

b

Median OS:
— Triple-negative MBC:
   234 days (95% CI: 263–293)
— Her2/ER-positive MBC:
   308 days (95% CI: 279–338)

P = 0.025

+ Censored

Median OS:
Brain metastases present:
221 days (95% CI: 167–274)
No brain metastases:
279 days (95% CI: 243–314)

P = 0.06

+ Censored

Median OS:
— > 2 prior lines of chemotherapy:
   264 days (95% CI: 229–298)
— ≤ 2 prior lines of chemotherapy:
   328 days (95% CI: 264–385)
P = 0.042
+ Censored