Short Communication

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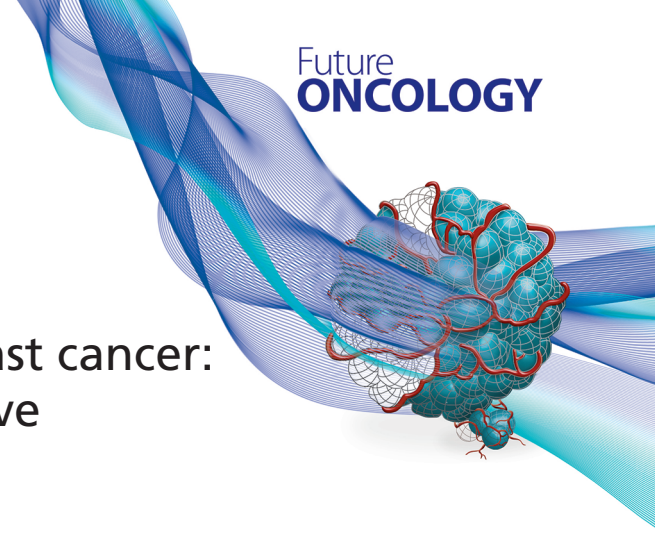

Eribulin in brain metastases of breast cancer: outcomes of the EBRAIM prospective observational trial

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Background: Eribulin shows some activity in controlling brain metastasis in breast cancer. **Methods:** This observational, multicenter study evaluated brain disease control rates, survival and safety in patients with brain metastatic breast cancer treated with eribulin in clinical practice. **Results:** A total of 34 patients were enrolled (mean age 49 years, 91% with visceral metastases) and 29 were evaluable for brain disease. Fourteen achieved disease control and showed a longer time without progression: 10 months (95% CI: 2.3–17.7) versus 4 months (95% CI: 3.3–4.7) in the control group (p = 0.029). Patients with clinical benefits at 6 months had longer survival. Leukopenia and neutropenia were the most frequent grade 3–4 toxicities. **Conclusion:** Eribulin confirms its effectiveness in patients with brain metastatic breast cancer. Further studies on larger cohorts are needed to confirm the results.

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Keywords: brain control rate • brain metastases • eribulin • metastatic breast cancer • observational trial

The increasing incidence of brain metastasis (BM) in patients with breast cancer (BC) [1] needs new therapeutic options. Eribulin mesylate is an inhibitor of mitosis [2,3] with *in vitro* proven antireplication activity against paclitaxel-resistant human ovarian cancer [4] as well as breast, colon and prostate cancers and melanoma [5]. It also shows antivascular activity that may contribute to vascular remodeling and facilitate the passage across the blood–brain barrier, especially after brain radiotherapy [6].

The efficacy and safety of treatments for metastatic BC have been explored in Phase I [7–10] and Phase II trials on multiple agents [11,12] and in anthracycline-resistant patients [13], with overall response rates ranging from 9.3 to 21.3% and median overall survival (OS) between 9 and 11.1 months. Neutropenia, leukopenia, fatigue, peripheral neuropathy and febrile neutropenia were the most common adverse events (AEs).

Phase III randomized controlled trials confirmed the efficacy and safety profile of eribulin on patients with locally advanced or recurrent BC. In the EMBRACE study, eribulin monotherapy significantly improved OS in patients with metastatic BC without BM, previously treated with at least two chemotherapy regimens, compared

with the treatment of physician's choice. In this study, peripheral neuropathy was the most frequent reason for discontinuation; 99% of patients experienced AEs, fatigue and neutropenia being the most common. One-fourth of the patients experienced a serious AE; five of the AEs were fatal [14]. In another Phase III trial, patients previously treated with taxanes or anthracyclines achieved a similar median OS (15.9 months) with eribulin or capecitabine; in this trial, the main AEs were diarrhea, nausea, vomiting, tiredness, asthenia, decreased appetite and peripheral sensory neuropathy [15].

In clinical practice, the results of eribulin treatment mirrored those of the randomized trials. A decade of clinical experience in the USA supports the clinical effectiveness of eribulin in patients with metastatic BC, including in patients with triple-negative BC [16]. The analysis of data from a large real-world database showed that eribulin in the third and fourth lines of treatment improved both progression-free survival (PFS) and OS compared with 'other chemotherapies', while in the second line the difference was not significant; these results were consistent in the subpopulation with CNS metastasis [17].

The results of a real-life multicenter study on 78 patients with metastatic BC, previously treated with at least two chemotherapy lines, highlighted that a 6-month treatment with eribulin was beneficial in 41% of the 18 patients with CNS metastases, independent of their biological subtype and the number of metastases. Alopecia, neutropenia and leukopenia were the most common AEs [18]. Another study including 95 patients (20 with BM) described the effectiveness of eribulin on the CNS, with four BM patients (20%) showing a partial response and five achieving stable disease; the disease control seemed to be independent from previous CNS local treatment [19]. Other anecdotal cases describe a certain activity of eribulin on BM [20–22].

To date, no studies have been designed to specifically evaluate the activity of eribulin in BM from BC. Therefore this study aims to evaluate the activity of eribulin in brain metastatic BC (BMBC) patients in daily clinical practice and in accordance with the regulatory authorities' indication of the drug [22,23].

Patients & methods

The EBRAIM study was a prospective, multicenter, observational trial conducted in six Italian oncological centers. Patients older than 18 years with a histological diagnosis of invasive BC with BM, diagnosed using a 1.5- or 3-Tesla MRI and previously treated with at least one line of chemotherapy for advanced disease, were included in the study after providing their consent to participate. Inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 [24]; neutrophils >1500/ml, platelets $>100{,}000$/ml, bilirubin <2 mg/dl, transaminase value less than two-times the upper normal limit, creatinine <1.5 mg/dl and a life expectancy of at least 3 months; only patients without other uncontrolled diseases or psychiatric disorders that could interfere with data collection were considered for inclusion. Pregnancy and breastfeeding status were checked before starting the study. Patients taking corticosteroids to control brain disease and patients with leptomeningeal metastases were admitted as long as they had controlled neurological symptoms. The treatment with eribulin was decided as clinically appropriate by the referring physician before and independently from the inclusion in this trial, where concomitant anticancer therapies were not permitted. Patients with previous surgery or radiotherapy – whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) or Cyberknife for BM at least 6 months before starting the treatment with eribulin – and with documented progression in CNS metastases were allowed. Radiotherapeutic treatment for extracranial metastases, or systemic chemotherapy, biological or hormonal treatment had to be discontinued 28 days before the first eribulin administration. The study was conducted according to the Declaration of Helsinki and the International Committee on Harmonization guidelines for Good Clinical Practice. The study was approved by the local Ethical Committee.

Treatment schedule

Treatment with eribulin mesylate (1.23 mg/m^2 administered intravenously for 2–5 min on days 1 and 8 of every 21-day cycle) continued until disease progression, unacceptable toxicity, or a patient or physician request to discontinue. Grade 3 or 4 toxic effects were managed by dose modifications. Concomitant treatments that did not interfere with eribulin, including the use of bisphosphonates, were admitted.

Data retrieval

Demographics, medical history, BC history and tumor biology were collected for each patient at study entry; data regarding tumor grade and staging (tumor size and nodal involvement) were collected according to the tumor node metastasis classification system of the Union Internationale Contre le Cancer, and tumors were

histologically classified according to WHO criteria [25]. The expression of conventional biological factors such as estrogen and progesterone receptors, HER2 status and Ki-67 proliferation index were obtained from pathology reports. HER2 status was determined by using the HercepTest™ preparation kit (Agilent, CA, USA) and classified as follows: scores of 0 or 1+ were considered as negative, 2+ as equivocal and 3+ as positive. BC samples with a score of 2+ were tested by FISH to evaluate *HER2* amplification. In tumor cells, the ratio between the *HER2* gene signal and the chromosome 17 centromere enumeration probe should be at least 2:1 to describe gene amplification. Patients underwent brain MRI (1.5–3.0 Tesla) for CNS evaluation and thoracic–abdominal CT scan for extracranial assessment at baseline (within 15 days from entering the study) and every 12 weeks. Response to eribulin was evaluated according to the Response Assessment in Neuro-oncology (RANO) criteria [26] in brain metastasis and according to the modified Response Evaluation Criteria In Solid Tumors [27] for the extracranial disease. Toxicity was assessed every 2 weeks as per the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.02) [28]. Furthermore, any AE that occurred during the observation period was collected according to the Italian laws [29,30].

Statistical analysis

The primary objective of this observational, prospective study was the brain disease control rate (DCR): the sum of complete and partial responses and stability of disease. The secondary end points included brain PFS (time from the start of therapy to brain progression), brain clinical benefit (sum of responses and stability of disease over periods of 3 and 6 months), extracranial response rate, extracranial PFS (time from the start of therapy to progression of extracranial disease), OS (time from the start to the date of death for any cause) and the safety of treatment. The study aimed to enroll 50 patients. This sample size was based on our previous (unpublished) personal experience in a similar set of patients in which we observed a DCR equal to 55%. Assuming a DCR equal to 40%, the sample size should have allowed estimating such incidence rate with a standard error of 7%.

Descriptive statistics were used to summarize the characteristics of the study participants. The continuous variables were reported as median and range, while categorical variables were summarized as frequencies and percentages. Differences between variables were evaluated using Pearson's Chi-square, Fisher exact or Mann–Whitney test, as appropriate. PFS and OS were calculated by the Kaplan–Meier product limit method. PFS was the time elapsing from the start of eribulin therapy to the date of objective evidence of disease progression or death of patients with documented disease progression. OS was estimated from the first day of treatment with eribulin to the date of death for any cause. Progression and survival were censored at the time of the last visit in alive patients not progressing during the observation period. The log-rank test was used to assess differences between subgroups. The hazard ratios and their relative 95% CIs were estimated for each variable using the Cox univariate model and adopting the most suitable prognostic modality as a referent group. A multivariate Cox proportional hazard model was then conducted considering the variables significant at univariate analysis using stepwise regression (forward selection).

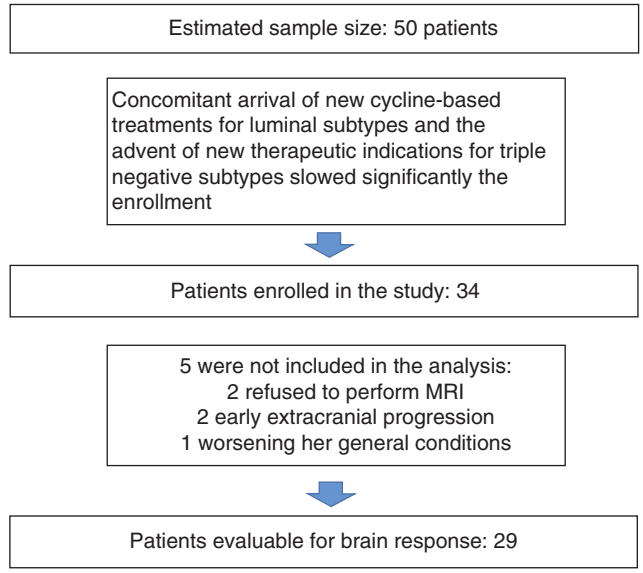

Figure 1. Enrollment and study design.

Enter limit and remove limit were set at p = 0.05 and p = 0.10, respectively. Significance was defined at the $p < 0.05$ level. All analyses were performed with SPSS v 21.0 (IBM Corp., NY, USA).

Results

Demographic & clinical characteristics

From December 2017 and January 2019, 34 patients were included in the study and were observed until August 2020; of these, 29 were evaluable for brain response (Figure 1). The median age was 49 years (range: 35–78); 20 patients (58.8%) had luminal B HER2$^-$ tumors, while 10 (29.4%) were triple negative. Twenty-seven (79.4%) patients had an ECOG performance status of 0 and six (17.6%) had a score of 1. Thirty-one patients (91.2%) had surgery for the primary breast tumor; 23 (67.7%) received adjuvant treatment, while only six (17.6%) received neoadjuvant treatment. Fifteen patients (44.1%) had three or fewer brain metastases and 16 (47%) had four or more at the start of the study. Two patients (5.8%) suffered from neoplastic leptomeningeal disease but showed an ECOG performance status of 0–1. Twenty-three (67.6%) patients received brain radiotherapy before eribulin treatment: WBRT (n = 12), median total dose 20 Gy; SRS (n = 7), Cyberknife (n = 3) and WBRT+SRS (n = 1) (Table 1). Three (13%) patients treated with WBRT achieved a partial response with a median duration of 5.7 months (range: 5.2–8.4), while four (57.1%) patients treated with SRS/Cyberknife obtained partial response lasting for a median of 6.8 months (range: 4.6–9.1).

There were no substantial differences in terms of brain involvement and biological subtype; two patients with meningeal diffusion had both a triple-negative and luminal B type BC.

Patients began the treatment with eribulin at a median of 68 months (range: 17–351) after their initial diagnosis. The number of metastatic sites ranged from one to five, and 91% of patients had visceral metastasis in addition to the brain lesions. Most patients (22/34; 65%) received eribulin as second- or third-line treatment (Table 1).

Outcomes

Twenty-nine patients were evaluable for brain activity, while five were not evaluable for activity (two refused MRI, two had early extracranial progressions and one experienced worsening of general conditions after the first cycle).

A total of 14 out of 29 (48.2%) patients achieved disease control, with two (6.9%) complete responses and two (6.9%) partial responses, giving an overall response rate of 13.8%; ten patients (34.5%) had stable disease according to RANO criteria (Figure 2A–C & Table 2). Clinical progression was observed in 15 patients (51.7%; Table 2). Among the 14 nonprogressing patients, ten (71.4%) had luminal B tumors. Luminal B tumors, in comparison with those belonging to the other molecular subtypes, showed a trend toward higher DCR – ten (62.5%) responders versus six (37.5%) non-responders – without reaching statistical significance.

Fourteen patients (41.1%) achieved a clinical benefit at 3 months, and seven (24.6%) at 6 months (Table 2).

Among two patients with neoplastic leptomeningeal disease, one achieved a partial response with a long duration (9.2 months) (Figure 2C).

A total of 17 out of 34 (50%) women reached disease control: three complete responses (8.8%), six partial responses (17.6%) and eight patients with stable disease (23.5%) (Table 2).

Efficacy

Brain progression-free survival

During the study, 24 new brain progressions occurred. The median time to a new brain progression after starting eribulin was 5 months (95% CI: 3.7–6.3) (Figure 3A). Kaplan–Meier estimates showed that patients achieving brain disease control had a longer time without a new progression than others: 10 months (95% CI: 2.3–17.7) versus 4 months (95% CI 3.3–4.7; p = 0.029) (Figure 3B). Furthermore, patients showing a clinical benefit at both 3 and 6 months had a longer time without a new brain progression: 11 months (95% CI: 5.5–16.5) versus 4 months (95% CI: 3.3–4.7; p = 0.003) and 11 months (95% CI: 8.6–13.4) versus 4 months (95% CI: 3.1–4.9; $p < 0.001$), respectively (Figure 3C & D). Cox regression results showed that the clinical benefit at 3 months played a role in predicting brain progression (hazard ratio: 0.24; 95% CI: 0.08–0.70; p = 0.009; Table 3).

Concerning extracranial progression, we observed 30 events during the study. From the start of Eribulin, the median time to disease progression was 4 months (95% CI: 3.3–4.7). Kaplan–Meier estimates showed that patients with extracranial progression achieving disease control had a longer time without a new progression than others: 5 months (95% CI: 1.4–8.6) versus 3 months (95% CI: 2.2–3.8; p = 0.001). Patients showing a clinical benefit at 3 and 6 months had a longer time without a new progression: 7 months (95% CI: 0–14.8) versus 3 months (95%

Table 1. Baseline demographic and clinical characteristics of the 34 patients enrolled in the EBRAIM study.

Characteristics	n (range or %)
Age at diagnosis (median, years)	49 (35–78)
Stage at diagnosis of tumor	
I	2 (6%)
II	12 (35%)
III	12 (35%)
IV	8 (24%)
HER2 status	
Negative	32 (94%)
Positive	2 (6%)
ER status	
Negative	12 (35%)
Positive	22 (65%)
PgR status	
Negative	14 (41%)
Positive	20 (59%)
Molecular subtype	
Lum A	2 (6%)
Lum B HER2-	20 (59%)
HER2-like	2 (6%)
Triple-negative	10 (29%)
ECOG performance status	
0	27 (79%)
1	6 (18%)
2	1 (3%)
Surgery on primary breast cancer	
Yes	31 (91%)
No	3 (9%)
Neoadjuvant chemotherapy	
Yes	6 (18%)
No	28 (82%)
Adjuvant chemotherapy	
Yes	23 (68%)
No	11 (32%)
Brain metastases (n)	
<3	15 (44%)
4–10	16 (47%)
>10	1 (3%)
Leptomeningosis	2 (6%)
Brain radiotherapy before eribulin	
Yes	23 (68%)
No	11 (32%)
Median time between diagnosis and start of eribulin treatment (months; n = 23)	6.5 (6–25)
Type of radiotherapy (n = 23)	
Cyberknife	3 (13%)
SRS	7 (30%)
WBRT	12 (52%)
WBRT+SRS	1 (5%)
Median time between diagnosis and start of eribulin treatment (months)	68 (17–351)

ECOG: Eastern Cooperative Oncology Group; ER: Estrogen receptor; Lum A: Luminal A; Lum B: Luminal B; SRS: Stereotactic radiosurgery; WBRT: Whole brain radiation therapy.

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Table 1. Baseline demographic and clinical characteristics of the 34 patients enrolled in the EBRAIM study (cont.).

Characteristics	n (range or %)
Median time between brain metastases and start of eribulin treatment (months)	4 (0–56)
Metastatic sites (including CNS) (median)	3 (1–5)
Metastatic sites (n)	
1–3	21 (62%)
>4	13 (38%)
Visceral metastasis (other than the brain)	
Yes	31 (91%)
No	3 (9%)
Eribulin line of treatment	
1	1 (3%)
2	11 (32%)
3	11 (32%)
4	11 (32%)

ECOG: Eastern Cooperative Oncology Group; ER: Estrogen receptor; Lum A: Luminal A; Lum B: Luminal B; SRS: Stereotactic radiosurgery; WBRT: Whole brain radiation therapy.

Table 2. Overall activity of eribulin and in the central nervous system.

Extracranial response	n (%)
Total evaluable patients	34
CR	3 (9)
PR	6 (17)
Overall response rate	9 (26)
SD	8 (23)
PD	17 (50)
Overall extracranial DCR	
CR + PR + SD	17 (50)
PD	17 (50)
Brain response[†]	
Total evaluable patients[†]	29
CR	2 (7)
PR	2 (7)
Overall response rate	4 (14)
SD	10 (34)
PD	15 (52)
Brain DCR[†]	
CR + PR + SD	14 (48)
PD	15 (52)
Clinical benefit at 3 months	
Yes	14 (41)
No	20 (59)
Clinical benefit at 6 months	
Yes	7 (21)
No	27 (79)

[†]not evaluable: five patients.
CR: Complete response; DCR: Disease control rate; PD: Progressive disease; PR: Partial response; SD: Stable disease.

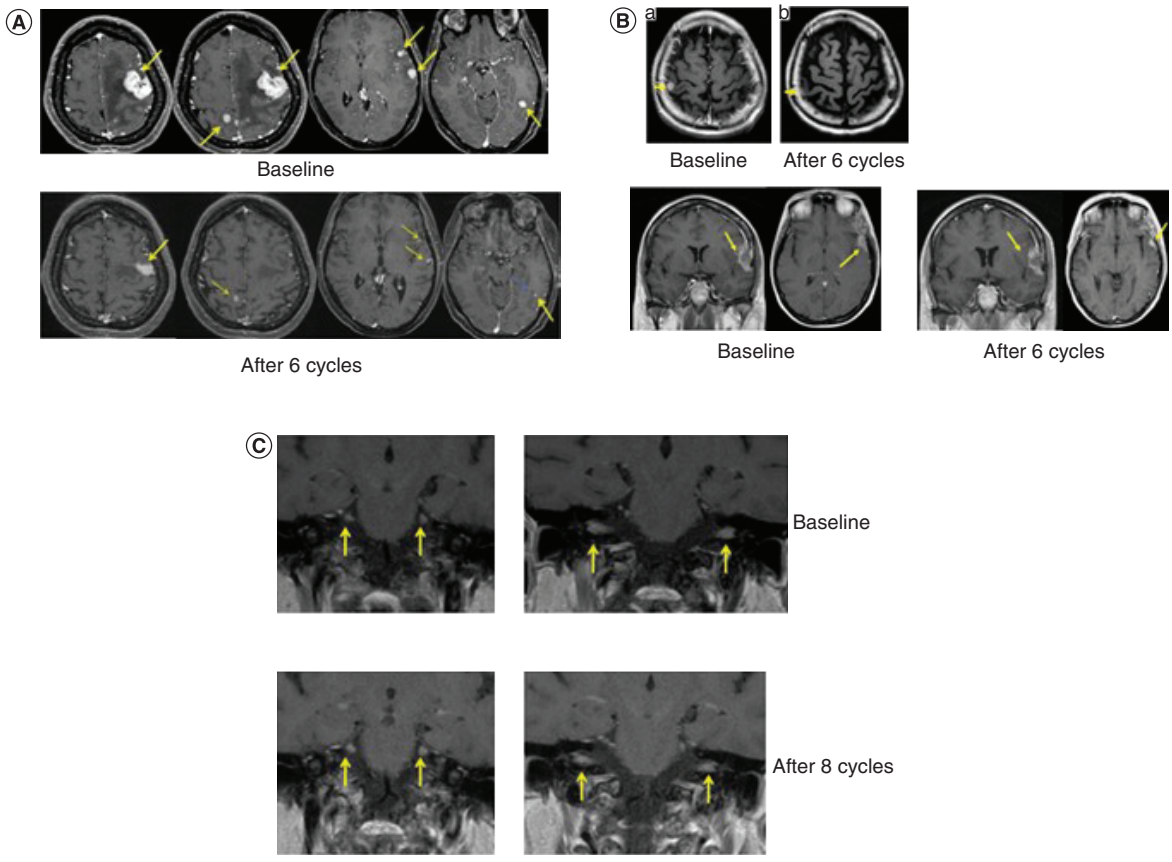

Figure 2. MRI evalutions of brain lesions. (A) Patient 1: MRI SE T1 sequences after contrast medium. MRI before treatment (baseline) shows the presence of multiple brain lesions in the right frontal and parietal lobes and the left temporal lobe, with significant edema for the bigger lesion. After six cycles a clear reduction in their size is shown after eribulin treatment. **(B)** Patient 2: MRI SE T1 sequences after contrast medium. MRI before treatment (baseline) shows the presence of a lesion in the right post-central lobe; there is an extra-axial lesion, with dural attachment in the frontal and temporal lobes. A marked reduction of the lesion in the postcentral lobe and the left frontal and temporal extra-axial lesion is visible after six cycles of eribulin. **(C)** Patient 3: MRI SE T1 sequences after contrast medium. MRI before treatment (baseline) shows an enlargement of the V, VII and VIII cranial nerves bilaterally as leptomeningeal lesions. The stable dimensions of the cranial nerves, showing enhancement of the lesions, are visible after eight cycles of eribulin.
SE: Spin echo.

Table 3. Progression-free survival (brain), progression-free survival and overall survival: Cox regression results.

Parameter	Comparison	PFS brain	PFS	OS
DCR brain	No vs yes	3.45 (1.25–9.55), 0.017	2.76 (1.17–6.48), 0.020	1.76 (0.73–4.34), 0.202
DCR overall	No vs yes	2.62 (1.00–6.84), 0.049	3.47 (1.43–8.40), 0.006	1.65 (0.72–3.80), 0.236
Stage at diagnosis	III + IV vs I + II	1.19 (0.49–2.88), 0.703	0.71 (0.33–1.51), 0.367	0.94 (0.40–2.32), 0.940
Subtype	HS + TN vs LUM	1.42 (0.61–3.35), 0.419	1.14 (0.53–2.45), 0.735	1.23 (0.54–2.81), 0.629
RT	No vs yes	1.51 (0.64–3.58), 0.350	1.49 (0.69–3.22), 0.316	2.38 (0.94–6.03), 0.067
Number of lines at eribulin administration	2+ vs 1–2	2.11 (0.86–5.14), 0.101	2.08 (0.94–4.62), 0.072	1.61 (0.67–3.90), 0.287
Number of sites extra brain	3+ vs <3	1.49 (0.64–3.49), 0.357	1.54 (0.72–3.30), 0.267	1.07 (0.48–2.39), 0.879
Clinical benefit at 3 months	No vs yes	0.24 (0.08–0.70), 0.009	0.20 (0.07–0.53), 0.001	0.46 (0.19–1.09), 0.078

Univariate analysis; results displayed as hazard ratio (95% CI), p-value.
DCR: Disease control rate; HS + TN: Hormone sensitive + triple negative; LUM: luminal; OS: Overall survival; PFS: Progression-free survival; RT: Radiotherapy.

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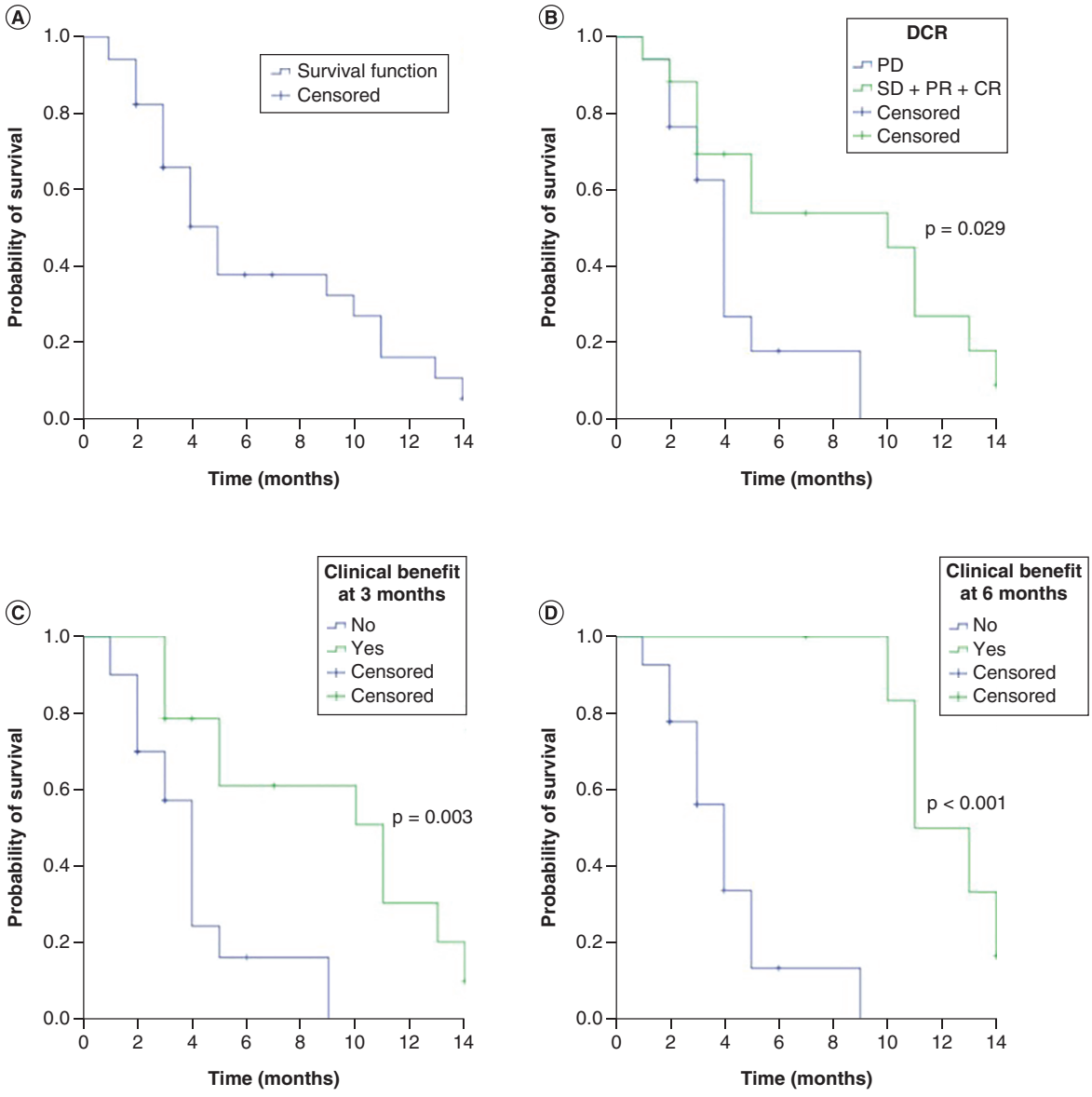

Figure 3. Progression-free survival of patients with brain metastases. Kaplan–Meier curves **(A)** on the overall population, **(B)** by DCR, **(C)** by clinical benefit at 3 months and **(D)** by clinical benefit at 6 months.
CR: Complete response; DCR: Disease control rate; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; SD: Stable disease.

CI: 2.2–3.8; $p < 0.001$) and 13 months (95% CI: 11.2–14.8) versus 3 months (95% CI: 2.4–3.6; $p < 0.001$), respectively.

PFS was significantly longer in patients who received eribulin after two lines of treatment than in those who were treated at or after three lines: 4 months (95% CI: 2.4–5.6) versus 3 months (95% CI: 2.4–3.6; $p = 0.037$). The Cox regression results showed that the clinical benefit at 3 months could predict extracranial progression (hazard ratio: 0.20; 95% CI: 0.07–0.53; $p = 0.001$) (Table 3).

Overall survival

We observed 26 events during the study period. The deaths occurred for the following reasons: 20 patients (76.9%) for CNS spreading, five (19.2%) for worsening of extracranial disease and one (3.8%) for pneumonia during the further chemotherapy line.

Table 4. Hematological and nonhematological toxicity.

Event	n (%)
Neutropenia	17 (50)
Leukopenia	24 (77.4)
Neutropenic fever	4 (11.8)
Anemia	2 (5.9)
Diarrhea	2 (5.9)
Increase of ALT/AST	3 (8.8)
Peripheral neuropathy	4 (11.8)
Asthenia	7 (20.5)
Anorexia	1 (2.9)
Alopecia	30 (88.2)

Grade 3–4 events in the 34 patients. Seventeen patients presented with complete alopecia before eribulin therapy.

From the start of eribulin treatment, the overall median time to death was 7 months (95% CI: 5.3–8.7). Kaplan–Meier estimates showed that patients receiving brain radiotherapy before eribulin died earlier than others: 6 months (95% CI: 3.9–8.1) versus 8 months (95% CI: 0.1–15.9; p = 0.045). Furthermore, patients who had any clinical benefit at 6 months had longer survival than those who did not show any clinical benefit: 16 months (95% CI: 13.9–18.1) versus 6 months (95% CI: 4.2–7.7; p < 0.001). The Cox regression results in Table 3 show that patients who had a DCR, both to brain and overall, and who had a clinical benefit at 3 months tended to have a longer survival.

Toxicity

All 34 patients experienced at least one event of grade 3–4 hematological toxicities: leukopenia, observed in 11 patients (33%) and neutropenia (10 patients; 29%) were the events most frequently reported. All other events, except alopecia, were observed in <10% of the patients (Table 4).

Discussion

In our cohort, the effect of eribulin in BMBC patients seems to confirm the evidence from previous studies [11,12,15,18]. Half of the observed women achieved disease control; consistently, DCR was 48% for BM. After 3 months, 41% of patients showed clinical benefit, half of them maintaining this achievement after 6 months. Patients reaching disease control had progression after a median of 10 months, significantly longer than observed in other patients. Furthermore, the median 11 months' PFS in patients achieving clinical benefit at 3 and 6 months was significantly longer than in other patients; the survival analysis highlighted that median OS was significantly longer in women who did not have any previous radiotherapy for BMs (8 months) than in others (6 months; p = 0.045). These goals were obtained with severe hematological AEs occurring in about one-third of patients; febrile neutropenia occurred in only four (5%), and no treatment-related fatal events were observed.

Due to the concomitant arrival of new cyclin-based treatments for luminal subtypes and the advent of new therapeutic indications for triple-negative subtypes, the enrollment slowed significantly, and we could enroll only 34 patients in six Italian specialized facilities, each following its usual clinical practice. The small sample size did not allow any multifactorial analysis or the identification of possible confounders or analysis by BC subgroups. The two patients whose BMs fully responded to the treatment both had luminal B type tumors. The analysis trying to identify a relationship between BM clinical response and possible predictors did not identify any clinical, cytological or demographic predictors of response.

The ORR observed in this sample of women (26%) was slightly higher than the one observed in previous studies using eribulin in similar patients [11,12], while the 6-month treatment benefit was achieved by a slightly lower ratio of women (7/34; 21%) than in a similar study (8/18; 41%) [15]. Thus the presence of BM seems not to influence the response to eribulin treatment in late-stage BC, while previous radiotherapy treatment of BM seems to reduce OS.

No differences were identified between the two more representative biological subgroups (luminal B and triple-negative tumors) in terms of brain DCR. These results confirmed that the localization of BMs does not influence

the response to eribulin treatment independently from the biological status of the tumor. For this reason, the biological characteristics and HER2/hormone receptor expression status of BMs should be studied to evaluate the heterogeneity between primary and secondary tumors and its possible correlation with the outcome of brain disease.

Patients who had received a previous radiotherapy treatment had a significantly shorter OS than others, suggesting that a greater activity of eribulin on lesions treated at an earlier stage is associated with better clinical features of the single patient. However, the difference in the OS may be related to the time needed for radiotherapy and to the best response achieved. Furthermore, eribulin has a peculiar mechanism of action when compared with other chemotherapeutics used in BC because of its high 'penetrability' in the brain, as demonstrated by its effectiveness in glioblastoma [31]. Few other drugs show an effect on brain lesions [31], and the evidence from eribulin studies suggests its use as first-line therapy on asymptomatic BM patients or after radiotherapy in symptomatic ones. Furthermore, given the certain role of the drug in the CNS, a subsequent step could be to test the drug in a larger population of patients with BM at the first recurrence of CNS disease.

The occurrence of severe hematological AEs and neutropenia was consistent with the results of similar [11,12,18] or controlled [13,14] studies using the same eribulin regimen, suggesting that the drug is tolerable also by patients who are heavily pretreated and who have widespread disease.

This is the first study having the main focus on the activity of eribulin in BM; this is particularly important because most of the clinical trials excluded patients with BC and BM due to their difficult management and the expected fatalities. Studies on BMBC are challenging because it is complex to homogeneously assess the disease state in patients who have poor general condition (ECOG performance status >2) and may require radiotherapy prior to the treatment; in this regard, the use of the RANO criteria may be advantageous. Furthermore, the DCR is a central parameter to evaluate the clinical outcomes of treatment in patients with BM because specific targets on brain disease are frequently lacking.

Considering the small sample and the different approaches from different oncological centers to the treatment of patients with metastatic BC progressing after previous cycles of chemotherapy, these results seem to confirm the available evidence, but must be cautiously taken into daily clinical practice. Further evidence should be collected from larger series, especially in patients at the first recurrence of brain disease.

Conclusion & future perspective

The results of this trial confirm the effectiveness of eribulin in women with metastatic BC previously treated with at least two chemotherapy regimens, regardless of biological subtypes and including patients with triple-negative BC. The ongoing analyses on data from pivotal trials will help to understand the incidence of new BMs in patients treated with eribulin and evaluate its potential protective effect, especially when compared with capecitabine and other chemotherapies usually used in these patients. These outcomes will permit the design of an *ad hoc* controlled study to identify the most effective use of eribulin in BCBM.

Summary points

- The increasing incidence of brain metastases in patients with breast cancer needs new therapeutic options.
- This study has been specifically designed to evaluate the activity of eribulin in these patients in daily clinical practice.
- Half of the observed women achieved brain disease control; consistently, the brain disease control rate was 48% for brain metastasis. After 3 months, 41% of patients showed clinical benefit, half of them maintaining this achievement at 6 months.
- Median progression-free survival in patients achieving clinical benefit at 6 months, was significantly longer than in patients who did not have any clinical benefit.
- Median overall survival was significantly longer in women who did not have any previous radiotherapy for brain metastases than in others.
- Eribulin confirmed its tolerability profile in patients who were heavily pretreated and had widespread disease, with hematological toxicities being the most frequent adverse events.

Author contributions

Conceptualization: A Fabi and I Terrenato; methodology: I Terrenato; formal analysis: I Terrenato; investigation: A Vidiri, V Villani, A Tanzilli, F Pedani, V Magri, M Palleschi, M Donadio, G Catania, C Nisticò, A Pace, M Maschio, M Airoldi, C Carapella, R Rudà, S Telera and F Cognetti; original draft preparation: A Fabi, I Terrenato; review and editing: A Vidiri, V Villani, A Tanzilli, F Pedani, V

Magri, M Palleschi, M Donadio, G Catania, C Nisticò, A Pace, M Maschio, M Airoldi, C Carapella, R Rudà, S Telera and F Cognetti; supervision: A Fabi and F Cognetti.

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Ethical conduct of research

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board. Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data availability statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to informed consent signed by the authors, not including their authorization to share their data.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Thulin A, Rönnerman E, Zhang C *et al.* Clinical outcome of patients with brain metastases from breast cancer – a population-based study over 21 years. *Breast* 50, 113–124 (2020).
2. Okouneva T, Azarenko O, Wilson L, Littlefield BA, Jordan MA. Inhibition of centromere dynamics by eribulin (E7389) during mitotic metaphase. *Mol. Cancer Ther.* 7, 2003–2011 (2008).
3. Jordan MA, Kamath K, Manna T *et al.* The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. *Mol. Cancer Ther.* 4, 1086–1095 (2005).
4. Kuznetsov G, TenDyke K, Yu K, Littlefield B. Antiproliferative effects of halichondrin B analog eribulin mesylate (E7389) against paclitaxel-resistant human cancer cells *in vitro*. *Mol. Cancer Ther.* 6(Suppl. 11), Abstract C58 (2007).
5. Towle MJ, Salvato KA, Budrow J *et al. In vitro* and *in vivo* anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. *Cancer Res.* 61, 1013–1021 (2001).
6. Catania G, Malaguti P, Gasparro S, Cognetti F, Vidiri A, Fabi A. Activity of eribulin mesylate in brain metastasis from breast cancer: a stone in a pond? *Oncology* 94, 29–33 (2018).
7. Goel S, Mita AC, Mita M *et al.* A Phase I study of eribulin mesylate (E7389), a mechanistically novel inhibitor of microtubule dynamics, in patients with advanced solid malignancies. *Clin. Cancer Res.* 15, 4207–4212 (2009).
8. Synold TW, Morgan RJ, Newman EM *et al.* A Phase I pharmacokinetic and target validation study of the novel anti-tubulin agent E7389: A California Cancer Consortium trial. *J. Clin. Oncol.* 23, 3036–3036 (2005).
9. Tan AR, Rubin EH, Walton DC *et al.* Phase I study of eribulin mesylate administered once every 21 days in patients with advanced solid tumors. *Clin. Cancer Res.* 15, 4213–4219 (2009).
10. Mukohara T, Nagai S, Mukai H, Namiki M, Minami H. Eribulin mesylate in patients with refractory cancers: a Phase I study. *Invest. New Drugs* 30, 1926–1933 (2012).
11. Aogi K, Iwata H, Masuda N *et al.* A Phase II study of eribulin in Japanese patients with: heavily pretreated metastatic breast cancer. *Ann. Oncol.* 23, 1441–1448 (2012).
12. Cortes J, Vahdat L, Blum JL *et al.* Phase II study of the halichondrin B analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine. *J. Clin. Oncol.* 28, 3922–3928 (2009).

13. Vahdat LT, Pruitt B, Fabian CJ *et al.* Phase II study of eribulin mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J. Clin. Oncol.* 27, 2954–2961 (2008).

14. Cortes J, O'Shaughnessy J, Loesch D *et al.* Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a Phase 3 open-label randomised study. *Lancet* 377, 914–923 (2011).

•• **Describes a pivotal trial that led to eribulin approval.**

15. Kaufman PA, Awada A, Twelves C *et al.* Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. *J. Clin. Oncol.* 33, 594–601 (2015).

•• **Describes a pivotal trial that led to eribulin approval.**

16. Mougalian SS, Kish JK, Zhang J, Liassou D, Feinberg BA. Effectiveness of eribulin in metastatic breast cancer: 10 years of real-world clinical experience in the United States. *Adv Ther.* 38(5), 2213–2225 (2021).

17. Jacot W, Heudel PE, Fraisse J *et al.* Real-life activity of eribulin mesylate among metastatic breast cancer patients in the multicenter national observational ESME program. *Int. J. Cancer* 145(12), 3359–3369 (2019).

18. Fabi A, Moscetti L, Ciccarese M *et al.* Eribulin in heavily pretreated metastatic breast cancer patients and clinical/biological feature correlations: impact on the practice. *Future Oncol.* 11, 431–438 (2015)

19. Sirvén MB, Fernández-Ortega A, Stradella A *et al.* Real-world efficacy, and safety of eribulin in advanced and pretreated HER2-negative breast cancer in a Spanish comprehensive cancer center. *BMC Pharmacol. Toxicol.* 20(1), 68 (2019).

20. Chang AY, Ying XX. Brain metastases from breast cancer and response to treatment with eribulin: a case series. *Breast Cancer Basic Clin. Res.* 9, 19–24 (2015).

21. Do Byun K, Ahn SG, Baik HJ *et al.* Eribulin mesylate combined with local treatment for brain metastasis from breast cancer: two case reports. *J. Breast Cancer* 19, 214–217 (2016).

22. Pean E, Klaar S, Berglund EG *et al.* The European Medicines Agency review of eribulin for the treatment of patients with locally advanced or metastatic breast cancer: summary of the scientific assessment of the committee for medicinal products for human use. *Clin. Cancer Res.* 18, 4491–4497 (2012).

23. US FDA.2010 Notifications. www.fda.gov/drugs/resources-information-approved-drugs/2010-notifications

24. Eastern Co-operative Oncology Group. ECOG Performance Status. https://ecog-acrin.org/resources/ecog-performance-status

25. WHO. *WHO Classification of Tumours of the Breast.* Volume 4. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Breast-2012

26. Chamberlain M, Junck L, Brandsma D *et al.* Leptomeningeal metastases: a RANO proposal for response criteria. *Neuro Oncol.* 19, 484–492 (2017).

27. Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* 45, 228–247 (2009).

28. Schoen MW, Basch E, Hudson LL *et al.* Software for administering the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events: usability study. *JMIR Hum. Factors* 16, e10070 (2018).

29. Italian Medicines Agency. Implementation of Directive 2001/83 / EC (and subsequent amending directives) relating to a Community code concerning medicinal products for human use, as well as Directive 2003/94/EC. (2006). www.agenziafarmaco.gov.it/sites/default/files/DL_2006_219_0.pdf

30. Italian Medicines Agency. Guideline for the classification and managing of observational studies on drugs (2008). www.gazzettaufficiale.it/eli/id/2008/03/31/08A02109/sg

31. Takahashi M, Miki S, Fujimoto K *et al.* Eribulin penetrates brain tumor tissue and prolongs survival of mice harboring intracerebral glioblastoma xenografts. *Cancer Sci.* 110, 2247–2257 (2019).

• **Describes the preclinical rationale for the use of eribulin in patients with brain metastatic breast cancer.**