Phase II, Multicenter, Single-arm Trial of Eribulin as First-line Therapy for Patients With Aggressive Taxane-pretreated HER2-Negative Metastatic Breast Cancer: The MERIBEL Study

Vanesa Ortega,[1,2] Antonio Antón,[3] Isabel Garau,[4] Noemia Afonso,[5] Lourdes Calvo,[6] Yolanda Fernández,[7] María Martínez-García,[8] Esperanza Blanco,[9] Pilar Zamora,[10] Mirta García,[11] José Juan Illarramendi,[12] César Augusto Rodríguez Sánchez,[13] Miguel Sampayo,[14] Elena Aguirre,[14] José Manuel Pérez-García,[14,15] Javier Cortés,[14,15,16,17,*] Antonio Llombart-Cussac[14,18,*]

Abstract

The purpose of the MERIBEL trial was to evaluate the efficacy and safety of eribulin monotherapy as first-line therapy for patients with aggressive taxane-pretreated HER2-negative metastatic breast cancer with a short disease-free interval. The median time to progression was 4.1 months, and the clinical benefit rate was 26.4%. These results confirm that eribulin represents an effective therapeutic option for this poor-prognosis population.

Background: Eribulin has efficacy in patients with progression after ≥ 1 chemotherapeutic regimen for metastatic breast cancer (MBC). A short disease-free interval (DFI) and previous use of taxanes in the neoadjuvant or adjuvant setting have been associated with worse outcomes for patients receiving first-line chemotherapy for HER2-negative MBC. The aim of the present trial was to evaluate the efficacy and safety of eribulin as first-line therapy for patients with HER2-negative MBC with these poor prognostic factors. **Patients and Methods:** Eribulin monotherapy was administered until disease progression or unacceptable toxicity. The principal selection criteria were HER2 negativity without previous chemotherapy for MBC, the previous use of taxanes for early-stage breast cancer, and a DFI of < 36 months (subsequently amended to 48 months). The primary endpoint was the investigator-assessed time to progression. The secondary endpoints included overall survival, progression-free survival, objective response rate, clinical benefit rate, duration of response, and toxicity profile. A total of 53 patients were enrolled and received ≥ 1 dose of eribulin. **Results:** The median patient age was 47 years (range, 23-82.8 years). The median DFI was 15.7 months (range, 0.1-46.4 months). The median investigator-assessed time to progression was 4.1 months (range, 0.2-27.8 months; 95% confidence interval, 3.2-6.2 months). The objective response and clinical benefit rate was 20.8% and 26.4%, respectively. All-grade and grade 3/4 adverse events developed in 96.2% and 69.8% of

*Javier Cortés and Antonio Llombart-Cussac contributed equally to this work.

[1]Hospital General de Granollers, Barcelona, Spain
[2]Hospital Vall d'Hebron, Barcelona, Spain
[3]Hospital Miguel Servet, Zaragoza, Spain
[4]Hospital Son Llatzer, Palma de Mallorca, Spain
[5]IPO Porto, Porto, Portugal
[6]Complejo Hospitalario Universitario A Coruña, A Coruña, Spain
[7]Hospital Central de Asturias, Oviedo, Spain
[8]Hospital del Mar, Barcelona, Spain
[9]Hospital Universitario Infanta Cristina, Badajoz, Spain
[10]Hospital Universitario La Paz, Madrid, Spain
[11]Hospital Insular de Las Palmas, Las Palmas de Gran Canaria, Spain
[12]Hospital General de Navarra, Pamplona, Spain
[13]Hospital Universitario de Salamanca IBSAL, Salamanca, Spain
[14]Medica Scientia Innovation Research (MedSIR), Barcelona, Spain
[15]IOB Institute of Oncology, Quironsalud Group, Madrid and Barcelona, Spain
[16]Ramon y Cajal University Hospital, Madrid, Spain
[17]Vall d'Hebron Institute of Oncology, Barcelona, Spain
[18]Hospital Arnau de Vilanova, Valencia, Spain

Submitted: Mar 8, 2017; Revised: Nov 22, 2018; Accepted: Dec 12, 2018; Epub: Dec 20, 2018

Address for correspondence: Antonio Llombart-Cussac, MD, Medica Scientia Innovation Research (MedSIR), Rambla de Catalunya 2, 2D, Barcelona 08007, Spain
E-mail contact: antonio.llombart@medsir.org

1526-8209/$ - see frontmatter
https://doi.org/10.1016/j.clbc.2018.12.012

patients, respectively. The most common treatment-related adverse events were neutropenia, leukopenia, alopecia, nausea, and anemia. **Conclusion:** Eribulin is effective and safe as first-line therapy for aggressive taxane-pretreated HER2-negative MBC.

Clinical Breast Cancer, Vol. 19, No. 2, 105-12
Keywords: Aggressive taxane-pretreated patients, Eribulin, First-line chemotherapy, HER2-negative, Metastatic breast cancer

Introduction

Metastatic breast cancer (MBC) is a treatable, but incurable, disease. The goal of care for MBC is to optimize both the length and the quality of life. However, recent advances in breast cancer research have allowed the deconstruction of the molecular profiles of breast cancer, leading to an increase in the treatment options, including more personalized therapy and considerable improvement in patient outcomes.[1,2] The treatment choice for patients with MBC should consider all the following factors[3]: hormone-receptor (HR) and HER2 status, previous therapies and toxicities, disease-free interval (DFI), tumor burden (defined as the number and site of metastases), Eastern Cooperative Oncology Group performance status, comorbidities (including organ dysfunctions), menopausal status, the need for rapid disease and symptom control, psychological factors, and patient preference.

Endocrine treatment has been the preferred option for patients with HR-positive/HER2-negative MBC in the first-line setting, alone or combined with cyclin-dependent kinase 4/6 inhibitors, even in the presence of visceral disease.[4,5] In this tumor subtype, chemotherapy should be reserved for cases of rapidly progressive disease, life-threatening disease, or proven endocrine resistance.[6,7] However, chemotherapy remains the mainstay of treatment for patients with triple-negative and HER2-positive MBC.[8,9]

For patients with HER2-negative MBC who are candidates for first-line chemotherapy, taxanes and anthracyclines have been the standard front-line treatment.[10] Sequential monotherapy has resulted in overall survival (OS) similar to that with combination therapy, with less toxicity.[11] Nevertheless, anthracyclines and taxanes have been frequently used as neoadjuvant or adjuvant therapy; thus, the number of patients previously exposed to these agents by the time MBC has developed has been increasing.

The effectiveness of repeat treatment with anthracyclines and taxanes in the advanced setting will be conditioned by the interval that has elapsed from the end of adjuvant therapy to the diagnosis of recurrence.[12] Patients in whom postadjuvant recurrence has developed in the first year are considered to have refractory disease or a high risk of resistance. A second patient group with disease resistance that has been poorly defined includes patients with relapse between the first and second or third year after adjuvant treatment. These patients can be considered to have an intermediate risk of resistance. Presumably, mechanisms of intrinsic resistance to adjuvant chemotherapy exist in both situations. Therefore, the clinical management for these patients should consider the use of alternative drugs to anthracyclines and taxanes.

Eribulin is a synthetic analogue of halichondrin B and is a non−taxane microtubule dynamic inhibitor. Eribulin is currently indicated in Europe for patients with locally advanced breast cancer or MBC progression after $\geq$ 1 chemotherapeutic regimen for advanced disease. The chemotherapeutic regimen should have included an anthracycline and a taxane in either the adjuvant or metastatic setting, unless the patient was not suitable for these agents.[13,14] In preclinical models, it has been shown that taxane-resistant cell lines remain sensitive to eribulin[15]; thus, eribulin could be an optimal choice for patients with taxane-resistant MBC. However, although all the clinical trials evaluating eribulin for MBC included patients previously treated with taxanes, none has specifically assessed whether these patients were resistant to taxanes.[14,16-18]

The aim of the present trial was to evaluate the efficacy and safety of eribulin as first-line therapy for patients with aggressive taxane-pretreated HER2-negative MBC with a short DFI.

Patients and Methods

Patients

The inclusion criteria were histologically confirmed HER2-negative locally recurrent breast cancer or MBC; no previous cytotoxic therapy for MBC; and treatment in the neoadjuvant or adjuvant setting with $\geq$ 1 taxane-based regimen (4 cycles of 3-week cycles of docetaxel or paclitaxel or 12 weeks of paclitaxel or nab-paclitaxel, weekly). Previous endocrine therapy for MBC was allowed. Patients were required to have had a DFI of a maximum of 36 months after completion of taxane-based therapy. A subsequent protocol amendment allowed the inclusion of patients with a DFI of a maximum of 48 months. Additional inclusion criteria were age $\geq$ 18 years; measurable or evaluable disease using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; Eastern Cooperative Oncology Group performance status of 0 or 1; adequate renal, hepatic, and hematologic function; and life expectancy $>$ 3 months.

Patients with de novo MBC were excluded. Patients were also excluded if they had a history, or radiographic evidence, of central nervous system disease (brain metastases or leptomeningeal disease); another cancer except for basal cell carcinoma of the skin; squamous cell carcinoma of the skin or in situ cervical cancer within the previous 3 years; major surgery or a significant traumatic injury within the previous 4 weeks; or a medical condition that was serious and/or not properly controlled. In addition, patients were excluded if they were currently receiving chronic treatment with systemic corticosteroids or other immunosuppressive drugs. Concurrent administration of bisphosphonates or anticoagulant agents was allowed.

The local institutional review boards approved the protocol. All the patients provided written informed consent before screening. The present study was registered in the ClinicalTrials.gov database (ClinicalTrials.gov identifier, NCT02061085).

Table 1 Patient Characteristics (n = 53)

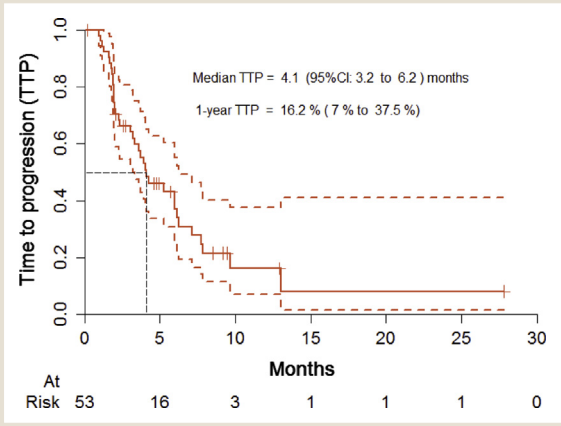
Characteristic	n, %
Age, y	
Median	47
Range	23-82.8
Women	53 (100.0)
ECOG performance status	
0	27 (50.9)
1	26 (49.1)
Luminal phenotype (ER-positive/PR-positive)	29 (54.7)
Triple-negative	24 (45.3)
Previous hormone therapy	
Yes	21 (39.6)
Neo- or adjuvant setting	21 (39.6)
Metastatic setting	6 (11.3)
No	32 (60.4)
Previous adjuvant chemotherapy	
Taxanes	53 (100.0)
Taxanes and anthracyclines	45 (84.9)
Disease-free interval,[a] mo	
Median	15.7
Range	0.1-46.5
> 24 mo	19 (35.8)
≤ 24 mo	34 (64.2)
Stage at study entry	
Locally recurrent	3 (5.7)
Metastatic	50 (94.3)
Organs involved[b]	
1	28 (52.8)
2	19 (35.8)
≥ 3	6 (11.3)
Metastatic disease site	
Visceral	28 (52.8)
Soft tissue	23 (43.4)
Most common metastatic site	
Soft tissue	23 (43.4)
Lung	21 (39.6)
Bone	18 (34.0)
Liver	14 (26.4)
Mediastinum	3 (5.7)
Other	3 (5.7)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; PR = progesterone receptor.
[a]Defined as the interval from the last taxane cycle to the first diagnosis of locally recurrent or metastatic disease (radiologic or histologic diagnostic) but not the interval between the advanced disease diagnosis and inclusion in the present study.
[b]Skin, lymph node, ipsilateral or contralateral breast, or other soft tissue involvement was scored as a single organ.

Study Design

All the patients received single-agent eribulin mesylate 1.4 mg/m^2 (equivalent to 1.23 mg/m^2 of eribulin expressed as free base) as a 2- to 5-minute intravenous infusion on days 1 and 8 of a 21-day cycle until disease progression, unacceptable toxicity, investigator criteria, or patient decision. Eribulin dose adjustments during treatment were performed according to the approved summary of product characteristics.

Figure 1 Kaplan-Meier Estimates of Time to Progression (TTP) Showing the Proportion of Patients Without Progression Until a Particular Time (Solid Red Line) and 95% Confidence Intervals (Cis) (Dashed Lines). The Black Dashed Lines Cross at the Median Survival Estimation



The patients' clinical status, liver function, and serum creatinine levels were assessed before each cycle. A complete blood count was also obtained before each eribulin infusion. Toxic effects were graded at baseline and during subsequent visits using the National Cancer Institute's Common Criteria for Adverse Events, version 4.0.3.

Disease status was assessed using the RECIST, version 1.1, at baseline and every 3 cycles until disease progression using computed tomography or magnetic resonance imaging of the thorax, abdomen, and pelvis. The tumor response was required to be confirmed a minimum of 28 days after the initial response had been noted. No independent radiologic review was performed.

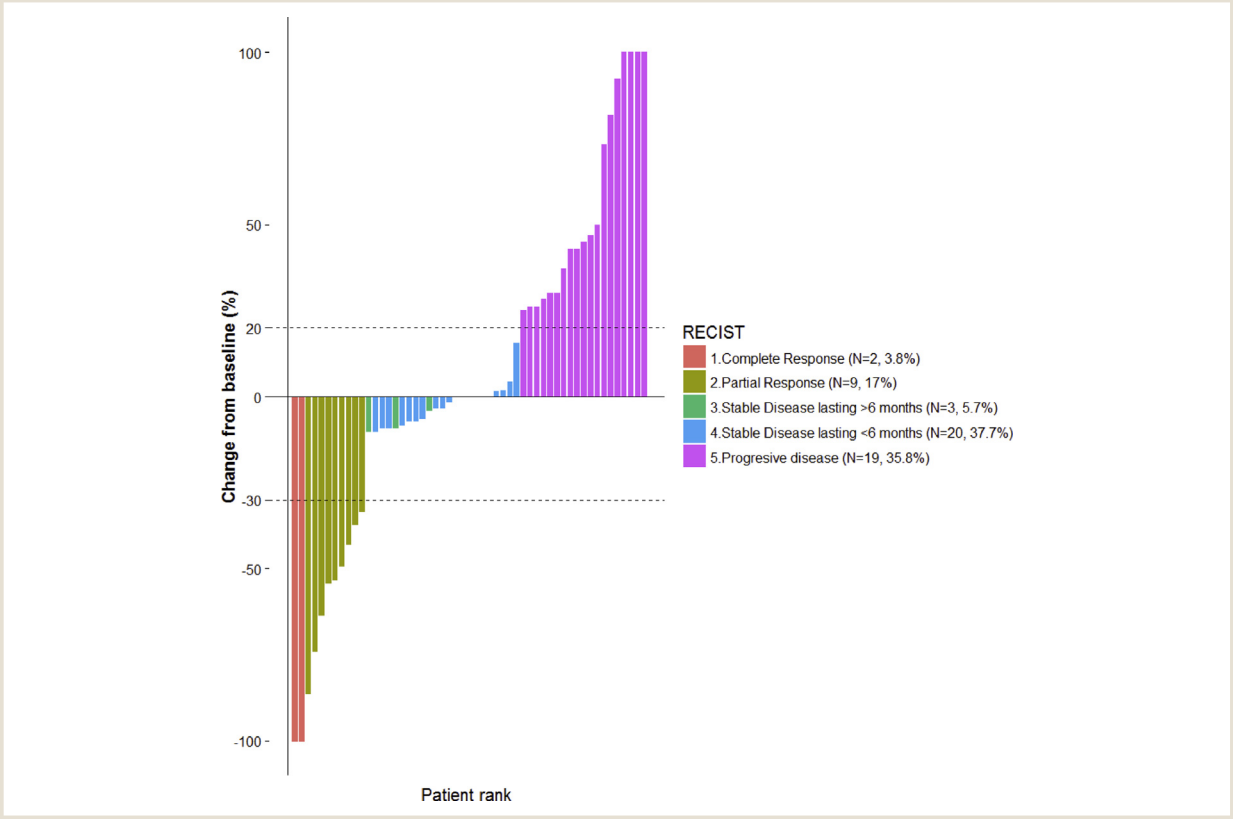
Study Objectives

The primary endpoint of the present study was the investigator-assessed time to progression (TTP). The TTP was defined as the interval from randomization until the first documented disease progression measured using the RECIST, version 1.1. The secondary objectives were OS (interval from randomization until death from any cause or the last date the patient was known to be alive), progression-free survival (PFS) (interval from randomization until the first documentation of disease progression or death from any cause), objective response rate (ORR) (partial response plus complete response), clinical benefit rate (CBR) (objective response plus stable disease for > 24 weeks), duration of response (DOR) (interval from the first documented objective response until disease progression or death from any cause), percentage of change from baseline in the tumor burden, and toxicity profile.

Statistical Analysis

A total of 60 patients were planned to be enrolled for the primary outcome. The sample size was determined for a single-arm time-

Figure 2 Waterfall Plot Showing Best Percentage of Change From Baseline in the Size of the Target Tumor Lesions



Abbreviation: RECIST = Response Evaluation Criteria in Solid Tumors.

to-event design. The trial had an 80% power to detect a 1.8-month increase in the median TTP during a median 3.7-month TTP (hazard ratio, 0.67).[13] The study protocol allowed for early termination because of futility or lack of efficacy of treatment at an interim analysis of the first 30 evaluable patients if the stopping boundaries had been crossed. To maintain an overall significance level of 0.05, spending for sequential analyses of TTP was determined using Lan-DeMets implementation of the O'Brien-Fleming boundaries. The 2-sided nominal significance levels of the interim and final analysis were $P = .0056$ and $P = .048$, respectively. The efficacy and safety analyses included data from all treated patients, including all those who had received ≥ 1 dose of eribulin.

The primary analysis was performed using the Kaplan-Meier method. For the secondary time-to-event efficacy endpoints (PFS, OS, and DOR), we used the same model used for the primary analysis, with the corresponding median and 95% confidence intervals (CIs). The binary efficacy endpoints (ORR and CBR) were estimated using the 95% Pearson-Clopper CIs.

As prespecified for the statistical analyses, exploratory analyses of the TTP according to the trial key baseline characteristics and safety endpoints were descriptively investigated using Cox proportional hazard regression analysis. The reported *P* values were 2-sided. They were only a descriptive tool to guide further analysis.

Results

Patient Population and Follow-up

The target sample size was not achieved because of slower than anticipated recruitment. The trial was stopped before the target sample size had been reached. Finally, 53 patients were enrolled and had received ≥ 1 dose of eribulin from September 2013 to March 2015. The patients were recruited from 12 sites and 2 countries. At the data cutoff point for the final analysis (December 2015), the median follow-up duration was 12.7 months (range, 0.2-30.5 months).

The median patient age was 47 years (range, 23-82.8 years). All the patients had been treated with neoadjuvant or adjuvant taxane-based chemotherapy in accordance with the protocol. Also, 45 patients (84.9%) had received anthracyclines in this setting. Of the 53 patients, 29 (54.7%) had HR-positive tumors and 24 (45.3%) had triple-negative tumors. Of the patients with HR-positive disease, 21 (72.4%) and 6 (20.7%) had received endocrine therapy for early and advanced disease, respectively. The median DFI was 15.7 months (range, 0.1-46.5 months). Of the 53 patients, 34 (64.2%) had had a DFI of ≤ 24 months. Of these 34 patients, 18 (34% of the overall population) had had a DFI of ≤ 12 months. The most common metastatic sites were soft tissue (43.4%), lung (39.6%), bone (34%), and liver (26.4%); 6 patients (11.3%) had ≥ 3 involved organ sites. The baseline characteristics of the patients are summarized in Table 1.

Table 2 Efficacy Analysis

Endpoint	n (%)
Primary	
TTP	36 (67.9)
Median	4.1
95% CI	3.2-6.2
Secondary	
Time to event	
PFS	36 (67.9)
Median	4.1
95% CI	3.2-6.6
1-y PFS rate	
Median	16.2
Range	7-37.5
OS,[a] mo	22 (41.5)
Median	NA
95% CI	NA
1-y OS rate	
Median	68.3
Range	56.5-82.5
Response evaluation	
ORR	11 (20.8)
95% CI	9.8-31.7
DOR, mo	
Median	4.5
Range	2.1-20.9
CBR	14 (26.4)
95% CI	14.5-38.3
DOR, mo	NA

Abbreviations: CI = confidence interval; CBR = clinical benefit rate; DOR = duration of response; NA = not achieved or not applicable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TTP = time to progression.
[a]Median follow-up was 12.7 months (range, 0.2-30.5 months).

Study Drug Exposure

The median number of cycles of eribulin received per patient was 6 (range, 1-41), and the median relative dose intensity per week was 91.6% (range, 55%-100%). Dose and schedule modifications were needed for 5 (9.4%) and 18 patients (34%), respectively. Dose reductions or delays were primarily required for neutropenia.

The main reason for treatment discontinuation was objective disease progression (36 patients; 67.9%). The other reasons for treatment discontinuation were adverse events (AEs) (7 patients [13.2%]), which included neutropenia, liver toxicity, neuropathy, rash acneiform, asthenia, ascites, and mild stroke not related to the drug; physician decision because of a lack of efficacy or clinical progression (6 patients; 11.3%); and patient decision (2 patients; 3.8%). At the end of the present study, 2 patients continued with eribulin treatment and 22 patients had died.

Efficacy Analyses

The results of the present study had not exceeded the futility or efficacy boundaries at the interim analysis. The median investigator-assessed TTP was 4.1 months (range, 0.2-27.8 months; 95% CI, 3.2-6.2 months; Figure 1). The 1-year TTP rate was 16.2% (95% CI, 7%-37.5%). No deaths were reported during eribulin treatment before the occurrence of radiologic progression. The median OS had not been reached after a median follow-up period of 12.7 months. The 1-year OS rate was 68.3% (95% CI, 56.5%-82.5%). The ORR was 20.8% (95% CI, 9.8%-31.7%). The overall response included 2 complete responses (3.8%) and 9 partial responses (17%). The CBR was 26.4% (95% CI, 14.5%-38.3%; Figure 2). The median DOR was 4.5 months (range, 2.1-20.9 months; 95% CI, 2.4-12.9 months). A summary of the efficacy analysis results is presented in Table 2.

Efficacy prespecified exploratory analyses were conducted to assess the effect of eribulin according to the selected predictive factors. A forest plot of the TTP subgroup analyses is shown in Figure 3. No statistically significant differences in the TTP were observed across all patient subgroups, although a longer median TTP was observed for patients with HR-positive tumors (6 vs. 3.9 months; $P = .111$) and patients with a DFI > 24 months (6.2 vs. 4 months; $P = .227$). In addition, although the median TTP was similar for patients with a DFI ≤ 12 or > 12 months, the 1-year OS rate was 0% for patients with a DFI of ≤ 12 months (n = 18).

The patients with grade 3/4 neutropenia and dose delays because of this toxicity had experienced greater antitumor activity compared with the patients without this AE. Those patients who had required dose delays also experienced a better median TTP (6 vs. 3.3 months; $P = .013$), median OS (not achieved vs. 6.4 months; $P = .019$), and ORR (38.9% vs. 11.4%; $P = .01$). However, those patients who had received ≤ 3 treatment cycles (n = 23) experienced a lower percentage of dose delays than those patients who had received > 3 cycles (n = 30; 13% vs. 50%; $P = .005$) (data not shown).

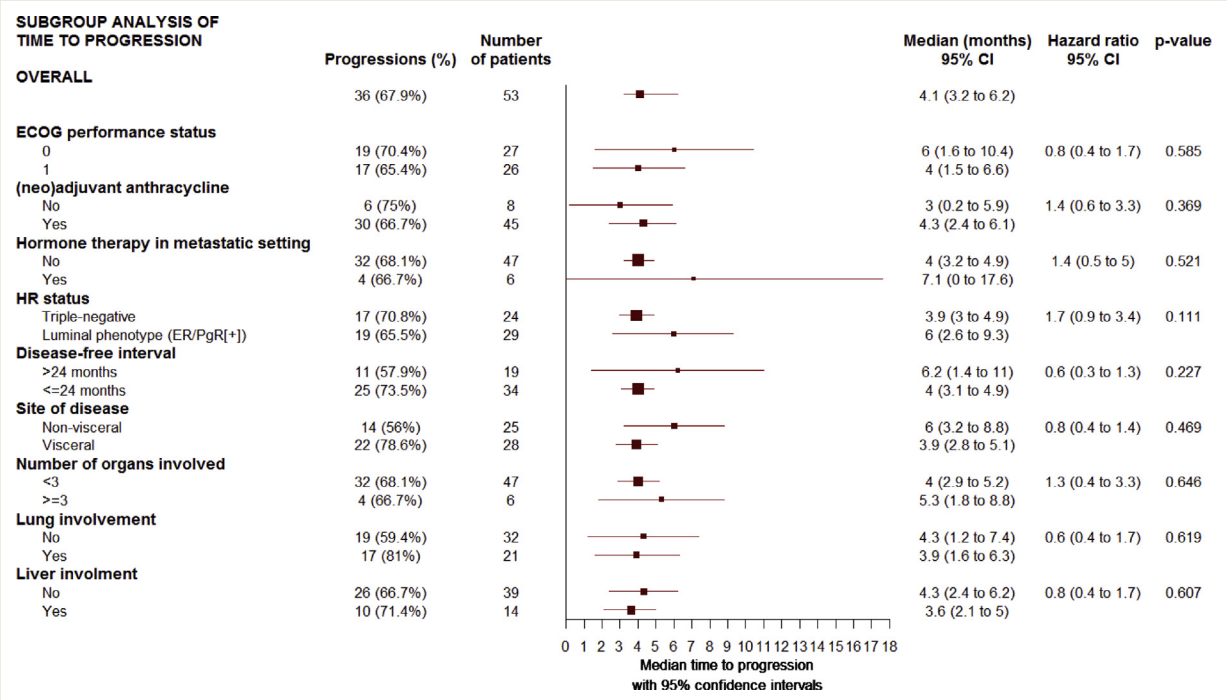
Safety Analyses

Eribulin showed a manageable tolerability profile with no unexpected safety signals. Eribulin-related AEs of all grades and grade 3/4 were reported in 51 patients (96.2%) and 37 patients (69.8%), respectively. The most common treatment-related AEs were neutropenia, leukopenia, alopecia, nausea, and anemia (Table 3). Neutropenia was the most common grade 3/4 treatment-related AE (35.9%), followed by leukopenia (17%). However, the incidence of febrile neutropenia was only 1.9%. Eribulin was associated with grade 3 neuropathy in 7.5% of the patients; no grade 4 neuropathy was reported. Serious AEs were observed in 11 patients (20.8%). Seven patients (13.2%) discontinued treatment because of AEs. However, the AE was not treatment related in 2 of these patients (pulmonary embolism related to disease progression and grade 1 stroke). No treatment-related deaths were reported.

Discussion

Until eribulin was approved, capecitabine was the only agent indicated in the United States and Europe for patients with disease resistance to both taxane and anthracycline regimens and patients with disease resistance to taxane or for whom anthracycline therapy was not indicated, with limited efficacy.[19] Ixabepilone has also been approved in the United States combined with capecitabine for patients without a treatment response to anthracyclines and taxanes.

Figure 3 Forest Plot for Subgroup Analyses of Time to Progression (TTP). Horizontal Bars Represent 95% Confidence Intervals (CIs) for the Median TTP in Each Subgroup. The Median TTP and Hazard Ratio Were Estimated Using the Kaplan-Meier Method and Cox Proportional Hazard Model, Respectively



Abbreviations: ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; HR = hormone-receptor; PgR = progesterone receptor.

However, the latter regimen has not been exempt from relevant toxicities.[20]

Eribulin has been recommended by most guidelines for patients with locally advanced or MBC who have received ≥ 1 previous chemotherapeutic regimens for advanced disease. The requirements include the use of an anthracycline and a taxane in the adjuvant or metastatic setting, unless the patient was not suitable for such treatment. The guidelines resulted from the survival benefit reported in the EMBRACE (image-guided intensity-modulated external beam radiochemotherapy and magnetic resonance imaging based adaptive brachytherapy in locally advanced cervical cancer) trial and the results of Study 301.[13,14]

The present phase II study evaluated the efficacy and safety of eribulin as first-line chemotherapy for patients with HER2-negative MBC and a short DFI after taxane-based chemotherapy in the neoadjuvant or adjuvant setting. The median TTP and CBR in our study (4.1 months and 26.4%, respectively) were equivalent to those observed in Study 301 with single-agent eribulin in patients with taxane-pretreated MBC (4.1 months and 26.2%, respectively). However, the patients included in Study 301 had received eribulin or capecitabine as their first-line (20%), second-line (50%), or third-line (30%) treatment of advanced or metastatic disease.[14] In contrast, most patients included in the MERIBEL trial presented with risk factors associated with poor outcomes according to previous studies (84.9% had received previous neoadjuvant or adjuvant treatment with anthracyclines and taxanes, ∼45% of the tumors were triple-negative, the median DFI was 15.7 months, and ∼65% of the patients had a DFI of ≤ 24 months). These findings could partially explain the similarity of our results compared with those from Study 301.[14,21,22] However, the 1-year OS rate for patients with a DFI of ≤ 12 months enrolled in the present trial was 0%. These patients will be considered to have taxane-refractory disease and will usually be excluded from first-line clinical trials, limiting their available therapeutic options.

The median OS was not been reached in the present study, at a median follow-up of 12.7 months. This endpoint for patients treated with first-line eribulin might be of particular interest because preclinical studies have demonstrated that eribulin induces vascular remodeling, increases oxygen flow to the tumor, reverses the epithelial-to-mesenchymal transition, and reduces the hypoxic conditions associated with an abnormal tumor microenvironment.[23,24] These mechanisms of action could explain why eribulin improved OS but not PFS in the EMBRACE trial.[13] Therefore, the findings from the phase III study comparing eribulin versus paclitaxel as first- or second-line therapy for patients with HER2-negative locally recurrent breast cancer or MBC will be of great interest because OS is the primary endpoint of that study (Clinical.Trials.gov identifier, NCT02037529).

No significant differences in the TTP were observed across all patient subgroups. However, as previously reported in other series, a longer median TTP was observed for patients with HR-positive tumors and for those with a DFI > 24 months.[21,22] Several studies

Table 3 Related Adverse Events

AE[a]	Total	Grade 1-2	Grade 3	Grade 4
Hematologic				
All	37 (69.8)	35 (66.0)	14 (26.4)	9 (17.0)
Neutropenia	31 (58.5)	30 (56.6)	10 (18.9)	9 (17.0)
Anemia	12 (22.6)	12 (22.6)	2 (3.8)	0 (0.0)
Febrile neutropenia	1 (1.9)	0 (0.0)	1 (1.9)	0 (0.0)
Thrombocytopenia	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)
Nonhematologic[a]				
All	39 (73.6)	39 (73.6)	14 (26.4)	4 (7.5)
Alopecia	18 (34.0)	18 (34.0)	0 (0.0)	0 (0.0)
Nausea	14 (26.4)	14 (26.4)	1 (1.9)	0 (0.0)
Constipation	11 (20.8)	10 (18.9)	2 (3.8)	0 (0.0)
Peripheral neuropathy	11 (20.8)	10 (18.9)	4 (7.5)	0 (0.0)
Anorexia	10 (18.9)	10 (18.9)	0 (0.0)	0 (0.0)
Asthenia	10 (18.9)	7 (13.2)	3 (5.7)	0 (0.0)
Abdominal pain	8 (15.1)	7 (13.2)	2 (3.8)	0 (0.0)
Paresthesia	7 (13.2)	7 (13.2)	1 (1.9)	0 (0.0)
Bone pain	6 (11.3)	5 (9.4)	2 (3.8)	0 (0.0)
Myalgia	6 (11.3)	5 (9.4)	1 (1.9)	0 (0.0)
Dry mouth	4 (7.5)	4 (7.5)	2 (3.8)	1 (1.9)
Increased alanine aminotransferase	2 (3.8)	1 (1.9)	1 (1.9)	1 (1.9)
Increased gamma-glutamyl transferase	2 (3.8)	0 (0.0)	0 (0.0)	2 (3.8)
Thromboembolic event	1 (1.9)	0 (0.0)	0 (0.0)	1 (1.9)

Data presented as n (%).
Abbreviation: AE = adverse event.
[a]If a patient had 2 AEs in the same system organ class or with the same preferred term with different Common Terminology Criteria for Adverse Events grades, the event with the highest grade was used for that patient.

have also shown a relationship between toxicity and the best tumor response in different cancer types.[25] From these findings, neutropenia has been identified as a predictive marker of response to chemotherapy in patients with advanced gastric and lung cancer.[26,27] In the present study, the TTP, OS, and ORR were better for patients with toxicity-related dose delays and grade 3/4 neutropenia. However, it is not clear whether the observed toxicity was predictive of the response to eribulin, because this finding would suggest that patients benefiting from longer treatment durations would be more prone to developing treatment-related AEs and patients with less treatment exposure due to a poor response, or no response, would experience less treatment-related toxicity. Therefore, caution is needed in the interpretation of the subgroup analysis results, in particular because the present study was exploratory, was conducted without any comparator, and had a reduced sample size that could have limited its external validity.

The reported treatment-emergent AEs were consistent with the known safety profile for eribulin. Eribulin had a manageable toxicity profile in the present study, similar to previous findings.[13,14,28] Neutropenia was the most common grade 3/4 treatment-related AE, although the rate of febrile neutropenia was very low. No treatment-related deaths were reported during the present study.

Conclusion

Eribulin monotherapy is active and safe as first-line therapy for patients with aggressive taxane-pretreated HER2-negative MBC with a short DFI. It will be essential in the near future to identify the potential biomarkers of the response to eribulin, understand the chemotherapy resistance mechanisms, and discover breast cancer druggable oncogenic alterations in this population to improve the treatment of patients with these poor prognostic factors.

Clinical Practice Points

- In patients with HER2-negative MBC who are candidates for first-line chemotherapy, taxanes and anthracyclines have been the standard front-line treatment.
- However, these agents have been frequently used as neoadjuvant or adjuvant therapy; consequently, the number of patients previously exposed to taxanes and anthracyclines by the time they have developed MBC has been increasing.
- A short DFI and previous use of taxane-based chemotherapy in the neoadjuvant or adjuvant setting have been associated with worse OS for patients receiving first-line chemotherapy for HER2-negative MBC.
- Thus, new therapeutic options are urgently needed for this poor-prognosis population.

- Eribulin—a synthetic analogue of halichondrin B—is a non−taxane microtubule dynamic inhibitor currently indicated in Europe for patients with locally advanced breast cancer or MBC with progression after ≥ 1 chemotherapeutic regimen for advanced disease.
- Eribulin has shown remarkable antitumor activity in taxane-resistant cell lines.
- The MERIBEL single-arm phase II trial has demonstrated that eribulin monotherapy is effective and safe as first-line therapy for patients with aggressive taxane-pretreated HER2-negative MBC with a short DFI after completing adjuvant taxane-based chemotherapy.
- Eribulin is currently being evaluated in a phase III study comparing eribulin and paclitaxel as first- or second-line therapy for patients with HER2-negative locally recurrent breast cancer or MBC previously treated with taxanes in the neoadjuvant or adjuvant setting.

Acknowledgments

The authors thank all the patients who participated in the MERIBEL trial, their families, the investigators, and the study teams. The present trial was sponsored by Medica Scientia Innovation Research SL (MedSIR), Barcelona, Spain. A grant for the present study was also provided by Eisai Farmacéutica SA, Madrid, Spain.

Disclosure

J.C. has received honoraria from Roche, Novartis, Celgene, Eisai, and Pfizer, has been a consultant for Roche, Celgene, AztraZeneca, Cellestia Biotech, and Biothera Pharmaceuticals in the previous 12 months, and has stock options for Medica Scientia Innovation Research SL (MedSIR). A.L.-C. has been a consultant for Roche, GlaxoSmithKline, Novartis, Celgene, Eisai, and AstraZeneca in the previous 12 months and has stock options for Medica Scientia Innovation Research SL (MedSIR). The remaining authors declare that they have no competing interests.

References

1. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature* 2012; 490:61-70.
2. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature* 2000; 406:747-52.
3. Cardoso F, Costa A, Norton L, et al. 1st International consensus guidelines for advanced breast cancer (ABC 1). *Breast* 2012; 21:242-52.
4. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016; 375:1738-48.
5. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016; 375:1925-36.
6. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Breast* 2014; 23:489-502.
7. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). *Ann Oncol* 2017; 28:16-33.
8. Baselga J, Cortés J, Kim S-B, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012; 366:109-19.
9. Gelmon K, Dent R, Mackey JR, Laing K, McLeod D, Verma S. Targeting triple-negative breast cancer: optimising therapeutic outcomes. *Ann Oncol* 2012; 23:2223-34.
10. Piccart-Gebhart MJ, Burzykowski T, Buyse M, et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. *J Clin Oncol* 2008; 26:1980-6.
11. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol* 2003; 21:588-92.
12. Palmieri C, Krell J, James CR, et al. Rechallenging with anthracyclines and taxanes in metastatic breast cancer. *Nat Rev Clin Oncol* 2010; 7:561-74.
13. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 2011; 377:914-23.
14. 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* 2015; 33:594-601.
15. Kuznetsov G, TenDyke K, Yu M, Littlefield B. Antiproliferative effects of halichondrin B analog eribulin mesylate (E7389) against paclitaxel-resistant human cancer cells in vitro. *Mol Cancer Ther* 2007; 6(suppl):C58.
16. Inoue K, Saito T, Okubo K, et al. Phase II clinical study of eribulin monotherapy in Japanese patients with metastatic breast cancer who had well-defined taxane resistance. *Breast Cancer Res Treat* 2016; 157:295-305.
17. 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* 2010; 28:3922-8.
18. 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* 2009; 27:2954-61.
19. Ershler WB. Capecitabine monotherapy: safe and effective treatment for metastatic breast cancer. *Oncologist* 2006; 11:325-35.
20. Sparano JA, Vrdoljak E, Rixe O, et al. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol* 2010; 28:3256-63.
21. Llombart-Cussac A, Pivot X, Biganzoli L, et al. A prognostic factor index for overall survival in patients receiving first-line chemotherapy for HER2-negative advanced breast cancer: an analysis of the ATHENA trial. *Breast* 2014; 23:656-62.
22. Goldhirsch A, Gelber RD, Castiglione M. Relapse of breast cancer after adjuvant treatment in premenopausal and perimenopausal women: patterns and prognoses. *J Clin Oncol* 1988; 6:89-97.
23. Yoshida T, Ozawa Y, Kimura T, et al. Eribulin mesilate suppresses experimental metastasis of breast cancer cells by reversing phenotype from epithelial-mesenchymal transition (EMT) to mesenchymal-epithelial transition (MET) states. *Br J Cancer* 2014; 110:1497-505.
24. Funahashi Y, Okamoto K, Adachi Y, et al. Eribulin mesylate reduces tumor microenvironment abnormality by vascular remodeling in preclinical human breast cancer models. *Cancer Sci* 2014; 105:1334-42.
25. Dienstmann R, Braña I, Rodon J, Tabernero J. Toxicity as a biomarker of efficacy of molecular targeted therapies: focus on EGFR and VEGF inhibiting anticancer drugs. *Oncologist* 2011; 16:1729-40.
26. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. Predictive value of chemotherapy-induced neutropenia for the efficacy of oral fluoropyrimidine S-1 in advanced gastric carcinoma. *Br J Cancer* 2007; 97:37-42.
27. Kishida Y, Kawahara M, Teramukai S, et al. Chemotherapy-induced neutropenia as a prognostic factor in advanced non-small-cell lung cancer: results from Japan Multinational Trial Organization LC00-03. *Br J Cancer* 2009; 101:1537-42.
28. Cortes J, Hudgens S, Twelves C, et al. Health-related quality of life in patients with locally advanced or metastatic breast cancer treated with eribulin mesylate or capecitabine in an open-label randomized phase 3 trial. *Breast Cancer Res Treat* 2015; 154:509-20.