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MERIBEL STUDY: EFFICACY OF ERIBULIN IN FIRST LINE OF TAXANE RESISTANT PATIENTS WITH HER2-NEGATIVE METASTATIC BREAST CANCER

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ABSTRACT

The main objective of the MERIBEL study is to determine the efficacy of eribulin as a single first-line agent for the treatment of patients with taxane-resistant, HER2-negative MBC. Secondary objectives are to assess treatment-related toxicity; evaluate the RECIST-based clinical response to treatment; and analyze clinical responses and tolerability with regards to hormone receptor status (+/-) and with regards to the presence, or absence, of visceral disease.

BACKGROUND

Eribulin is a non-taxane microtubule dynamics inhibitor which, in a phase III pivotal trial in women with pre-treated MBC, was shown to provide a significant benefit in overall survival compared to the study control arm (Cortes et al. 2011). However, little is known about the activity of this agent in early treatment lines in patients with taxane-resistant MBC. This trial is designed to determine the safety and efficacy of eribulin as single agent first-line treatment for patients with taxane-resistant HER2(-) MBC.

METHODS

Trial design

This is a phase IIa, multicenter, open-label, single-arm clinical trial in patients with HER2(-) MBC. The study regimen consists of the administration of 1,23 mg/m2 of eribulin (equivalent to 1.4mg/m2 eribulin mesylate) as a single agent on days 1 and 8 of each 21 day cycle, until disease progression, unacceptable toxicity, or investigator's decision (see figure 2, tables 1 and 2). The study was approved by the competent authorities and Ethics Committees from 14 participating sites in Spain and Portugal.

Statistical Methods:

- Primary endpoint: time to progression (TTP).
- Secondary endpoints: toxicity, treatment response rate, progression-free survival and overall survival.

Sample size: 60 patients. (H0): median TTP <3.7 versus (HA):> = 5.5 months.

(A error = 4.8% bilateral, Error β = 16%). Interim analysis of 30 completed patients. Intermediate α error: 0.5% (O'Brien Fleming).

CURRENT ENROLLMENT

Currently, 43 women have been accrued for the trial from 11 different sites and 2 countries (see figure 1).

Since the study start on July 2013, the enrollment has grown steadily (see graph 1) and it is expected to finalize by the end of January 2015. Currently, 30% of the 43 patients are still in the trial. Two of the patients (5%) have exceeded 12 months of treatment and as of today continue to receive the study regimen, while 25% have not yet completed the 12-month follow-up period (see graph 2).

ELIGIBILITY CRITERIA

The main inclusion and exclusion criteria were:

1	Patients with MBC that have not received prior chemotherapy for advanced or metastatic disease;
2	Previous chemotherapy for early stages (I-IIIB) including taxanes (paclitaxel and/or docetaxel) for at least 4 cycles;
3	Less than a span of 36 months between the last cycle of a taxane-based regimen in the adyuvant setting and disease relapse;
4	Evaluable disease based on RECIST criteria;
5	Absence of HER2 over-expression (IHQ of 0/1 or negative FISH/CISH);
6	Absence of neurotoxicity > G1 48 months prior to study entry.

Figure 1. Enrollment: The numbers display the enrollment for each site (Countries: Spain and Portugal, Southern Europe).

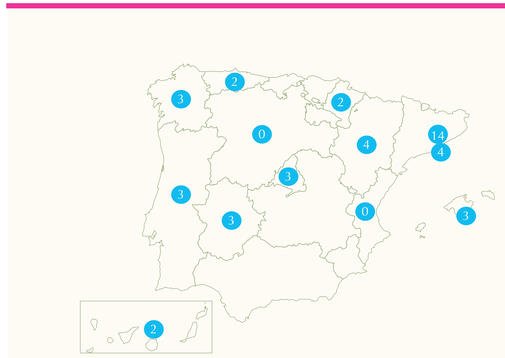
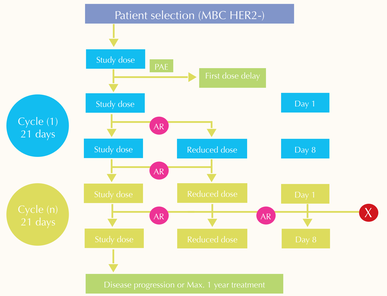


Table 1. Summary of dose delays at study initiation

Previous Adverse Event	Resolution
	Delaying the administration of eribulin until:
ANC < 1 x 10^9/l	ANC ≥ 1.5 x 10^9/l
Platelets < 75 x 10^9/l	Platelets > 100 x 10^9/l
No hematologic toxicities of grade 3 or 4	Non-hematologic toxicities disappearance or improvement to ≤ grade 2

(ANC: absolute neutrophil count): Summary of situations leading to a delayed administration of the first study dose. No further delays are allowed after initiation with the first study dose.

Figure 2. Study Schedule



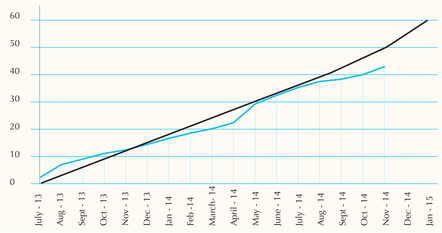
(MBC: metastatic breast cancer; PAE: previous adverse event; AR: adverse reaction):It depicts the cycles of treatment with the study drug as well as the possible variations from the same schedule. See Table 1 showing reasons for first dose delay, and see Table 2 displaying the dose reduction criteria. It also shows an early termination (marked with an X) and the study end.

Table 2. Summary of dose reductions during the study

Adverse Reaction	Resolution
Hematologic	Administration of 0.97 mg/m² (20% reduction of the study dose)
ANC < 0.5 x 10^9/l lasting longer than 7 days	
Neutropenia and ANC < 0.5 x 10^9/l plus fever or infection	
Trombocytopenia and platelets < 25 x 10^9/l	
Trombocytopenia and platelets < 50 x 10^9/l plus bleeding or requiring transfusion of blood or platelets	
Non-hematologic toxicities of grade 3 or 4 in previous cycles	
Recurrence of any adverse reactions previously described	Administration of 0.62 mg/m²
Recurrence of any adverse reactions previously described	Discontinuation

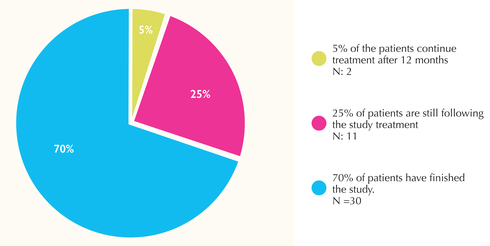
(ANC: absolute neutrophil count): Summary of situations leading to a reduction of the study dose.

Graph 1. Enrollment evolution



Enrollment evolution (blue line) is presented vs. target enrollment (black line)

Graph 2. Current status of the 43 accrued patients



DISCUSSION

There exists accumulated evidence regarding eribulin therapeutic efficacy in taxane-refractory / resistant tumor cells (Kuznetsov et al. 2007; Cortes et al. 2011). This evidence gave rise to the recent 2014 EMA approval for the use of eribulin in patients pretreated with a taxane, an anthracycline and at least one line of chemotherapy for metastatic breast cancer.

Therefore, it is reasonable to expect that eribulin may be a valid alternative for metastatic breast cancer patients that are not candidates for taxane treatment in first-line therapy. The MERIBEL study aims to assess this possibility.

REFERENCES

Cortes, J., J. O'Shaughnessy, et al. (2011). "Eribulin monotherapy versus treatment of physician's choice in patients with metastaticbreast cancer (EMBRACE): a phase 3 open-label randomised study." Lancet 377(9769): 914-23.

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