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A multicenter, randomized, phase II trial evaluating the efficacy of eribulin monotherapy and eribulin plus endocrine therapy in locally-recurrent or metastatic breast cancer patients after progression on endocrine therapy: REVERT study.

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BACKGROUND

- Previous studies have shown prolonged overall survival (OS) in patients with metastatic breast cancer (MBC) treated with eribulin, without a clear improvement in progression-free survival (PFS), which might indicate an eribulin-mediated suppression of further spread of metastasis.[1,2]

- In addition, it was shown that 44.1% of patients with luminal B-like tumors who received neoadjuvant eribulin converted to the luminal A-like subtype, which might be associated to a more endocrine-sensitive behavior.[3]

- The aim of this trial is to explore the efficacy of eribulin in combination with the same aromatase inhibitor (AI) administered in the last endocrine therapy (ET) regimen in patients who had previously shown progression while on an AI-containing regimen in the metastatic setting or within six months from their last AI dose in the adjuvant setting.

TRIAL DESIGN

- This is a multicenter, open-label, randomized, Simon's two-stage design, non-comparative phase II trial. Patients will be randomized in a 1:1 ratio to receive either eribulin in combination with the last AI administered in the metastatic or adjuvant setting (Arm A) or eribulin alone (Arm B). **(Figure 1)**.

- Patients will receive eribulin intravenously on days 1 and 8 of every 21-day cycle, in combination with exemestane, letrozole, anastrozole, or alone until disease progression, unacceptable toxicity or study withdrawal.

STUDY OBJECTIVES

- **PRIMARY OBJECTIVE**

To assess the efficacy -defined as overall response rate (ORR)- of eribulin in combination with AI (Arm A) in pre- and post-menopausal women with hormone receptor (HR)-positive (+)/ Human Epidermal Growth Factor Receptor 2 (HER2)-negative (-), unresectable locally advanced or MBC after progression on ET.

- **PRIMARY ENDPOINT**

- The proportion of patients in treatment Arm A with confirmed complete or partial response according to the Response Evaluation Criteria in Solid Tumors (RECIST) version (v.)1.1.

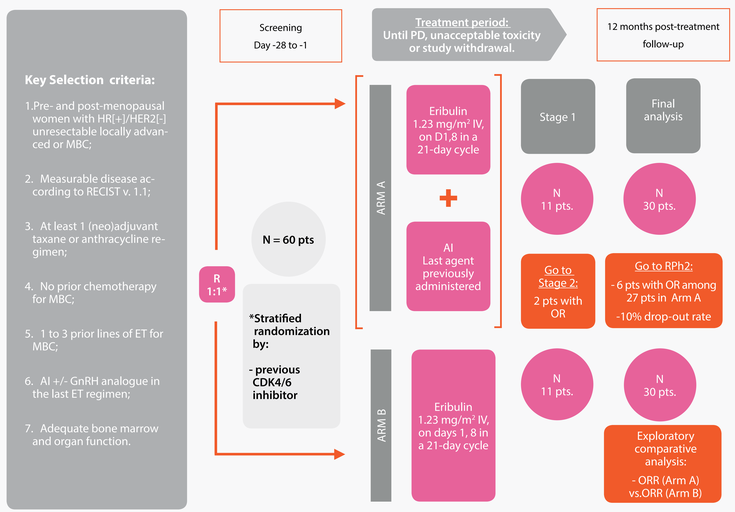
- **SECONDARY OBJECTIVES**

- To assess the efficacy of eribulin in combination with AI or in monotherapy -defined as PFS, OS, clinical benefit rate (CBR), duration of response (DoR), maximum tumor shrinkage (MTS) in both arms, and ORR in treatment Arm B;
- To determine safety-related outcome as per National Cancer Institute´s (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.5.0.

- **EXPLORATORY OBJECTIVE**

- To identify molecular patterns (gene signatures, mutational loads, etc.) which are predictive of sensitivity/resistance to eribulin (alone or in combination with ET) in the clinical practice.

FIGURE 1. Study Design



Endpoints

- Primary: ORR in Arm A as per RECIST v.1.1.
- Secondary: ORR in Arm B; PFS, OS, DoR, CBR, MTS in both Arms; Safety and tolerability as per NCI-CTCAE v.5.0.
- Exploratory: Molecular patterns of sensitivity/resistance.

AI: Aromatase inhibitor; CBR: Clinical benefit rate; CDK4/6: Cyclin-dependent kinases 4 and 6; DoR: Duration of response; ET: Endocrine therapy; GnRH: Gonadotropin-releasing hormone; HER2: Human Epidermal Growth Factor Receptor 2; HR: Hormone receptor; IV: Intravenous; m²: square meter; MBC: Metastatic breast cancer; mg: Milligrams; MTS: Maximum tumor shrinkage; N: Number of patients; NCI-CTCAE: National Cancer Institute's Common Terminology Criteria for Adverse Events; OR: Overall response; ORR: Overall response rate; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; Pts: Patients; R: Randomization; RECIST: Response Evaluation Criteria in Solid Tumors; RPh2: Randomized phase 2 comparative trial; v.: Version; vs: Versus.

STATISTICAL METHODS

Primary analysis

- Patients will be accrued in a Simon's two-stage admissible design.
- On the basis of an exact binomial distribution, approximately 27 patients were required in the Arm A to test a null hypothesis of an ORR ≤10% versus a target ORR of ≥30%, with a one-sided alpha of .05 and 80% power.
- Considering a drop-out rate of 10%, a sample size of 30 patients were preplanned in Arm A.
- In stage I, the accrual goal will be a total of 22 patients (11 patients in each Arm). If there are at least 2 responders out of 11 patients in Arm A, accrual will continue to stage II with 38 additional patients (19 patients in each Arm) until a total of 60 patients.
- At least 6 responders among 27 evaluable patients in Arm A will be adequate to justify the investigation of this strategy in further clinical trials.

Exploratory comparative analysis:

- Assuming an ORR of 30% in the combination arm and 10% in the monotherapy arm, a sample size of 60 subjects will provide a precision for the observed differences between arms with half width of two-sided 95% confidence interval (95%CI) of about 20%.

TRIAL ENROLLMENT

Currently, REVERT study is open and recruiting in 9 institutions from Spain. Patient recruitment started in 2Q19.

BIBLIOGRAPHY

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Conflicts of interest: https://medsir.org/revert/

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Trial Registration: NCT03795012 on January 7th, 2019. First patient included: June 24th, 2019.