

# NeoEribulin: A Phase II, non-randomized, open-label, single-arm, multicenter, exploratory pharmacogenomic study of single-agent eribulin as neoadjuvant treatment for operable Stage I-II HER2 non-overexpressing breast cancer

Aleix Prat<sup>1,3</sup>, Antonio Llombart<sup>2,3</sup>, Lorena de la Peña<sup>3</sup>, Serena Di Cosimo<sup>3,4</sup>, Vanesa Ortega<sup>1</sup>, Isabel Rubio<sup>1,3</sup>, Eva Muñoz<sup>1</sup>, Nadia Harbeck<sup>5</sup>, and Javier Cortés<sup>1,3</sup>

<sup>1</sup>Vall d'Hebron University Hospital, Barcelona, Spain; <sup>2</sup>Hospital Arnau de Vilanova, Valencia, Spain; <sup>3</sup>SOLTI Breast Cancer Research Group, Barcelona, Spain; <sup>4</sup>Istituto Nazionale dei Tumori, Milan, Italy; <sup>5</sup>Brustzentrum, Frauenklinik der Universität München, Germany

## BACKGROUND

- Chemotherapeutics, particularly microtubule inhibitors, are the backbone of most breast cancer treatment regimens. However, further research into new compounds is needed in order to provide additional options that maximize benefit, minimize toxicity, and most of all, deliver on the promise of personalized medicine.
- Eribulin is a nontaxane microtubule dynamics inhibitor with a novel mechanism of action<sup>1</sup> that has demonstrated to prolong OS in a Phase III metastatic breast cancer trial. Toxicity was manageable, including a modest incidence of neuropathy, which appears to be lower than that of other antimicrotubule agents<sup>2</sup>.
- Neoadjuvant trials provide a unique opportunity to rapidly assess the activity of novel compounds and to search for predictive biomarkers of response, without detriment to the patient<sup>3</sup>.
- Gene expression-based assays are becoming the norm in the current standard of care and are expected to supplement, and perhaps in some cases even replace, the single-biomarker approaches used in pathology analysis today<sup>3-5</sup>.
- This study aims to prospectively determine which patients, based on their molecular profiles, can derive the maximum benefit from treatment with eribulin.

## OBJECTIVES

### Primary

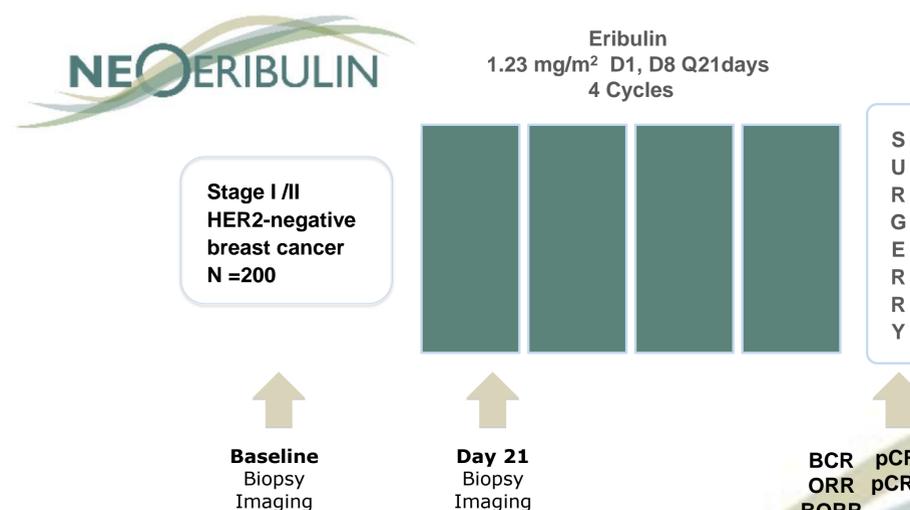
- To evaluate the correlation between pre-treatment mRNA expression profiles and clinical benefit from neoadjuvant eribulin, assessed by the rates of pathological complete response in the breast (pCR<sub>B</sub>).

### Secondary

- To assess clinical benefit, measured by the rates of pCR<sub>B</sub> and breast and axilla (pCR<sub>BL</sub>), as well as by overall response.
- To determine the correlation between pCR<sub>B</sub> with breast cancer subtypes as determined by IHC and by PAM50.
- To determine the biological activity of the treatment with eribulin, assessed by comparing gene expression at different time points and their correlation pCR<sub>B</sub> rate.
- To assess the rate of breast conserving surgery
- To estimate the sensitivity and specificity of the gene expression assay to predict clinical response
- To evaluate the safety and tolerability of the regimen
- To evaluate the role of tubulin isotype expression and mutational status in the response to therapy
- To identify other molecular biomarkers of response and/or safety

## KEY ELIGIBILITY CRITERIA

- Histologically confirmed invasive breast carcinoma with all of the following characteristics:
  - Primary tumor ≥2 cm in largest diameter (cT1-3)
  - Clinically evident axillary lymph nodes (cN0-1)
  - No evidence of distant metastasis (M0)
  - Eligible for definitive primary surgery
  - HER2 negative
- ECOG performance status of 0 or 1
- Multifocal tumors are allowed only if:
  - Largest lesion ≥2 cm
  - Well documented HER2- status in all tumor foci
  - ER/PgR status of the target lesion by IHC will be used to classify the breast cancer subtype



**Table 1** – Translational research

	Baseline		Day 21	Surgery
Type of sample	Core biopsy		Core biopsy	Surgical specimen (if available)
Material to be extracted	RNA	DNA	RNA	RNA
Assay	NanoString	Sequencing	NanoString	NanoString
Information to be captured	<ul style="list-style-type: none"> <li>Tumor mRNA expression profile</li> <li>Tumor mutational status</li> <li>Germ-line ("normal") DNA profile</li> </ul>		<ul style="list-style-type: none"> <li>Variations in mRNA expression profile due to treatment</li> </ul>	<ul style="list-style-type: none"> <li>Variations in mRNA expression profile due to treatment</li> </ul>

## METHODS

- This is a multicenter, single-arm exploratory phase II clinical trial of neoadjuvant eribulin for the treatment of primary HER2-negative breast cancer.
- As the purpose of this study is mainly the identification of biomarkers of response, multiple biospecimens will be collected:
  - Baseline, 21-day on-treatment, and post-treatment (see Table 1)
  - The expression of 542 genes involved in breast cancer will be explored with the NanoString technology using formalin-fixed, paraffin-embedded tissue.
  - The expression of single genes and the score of each signature in the pre-treatment and 21-day samples will be correlated with the clinical outcomes.
- Assuming an average pCR in the breast of 15%, a sample size of 200 patients is estimated to provide a 90% probability of detecting a gene signature whose expression is associated with a two-fold increase in odds of achieving a pCR in the breast, assuming 5% of patients would be lost to follow-up and 5% would have insufficient quality or quantity of mRNA.
  - The expected rate of pCR is calculated assuming the following values: 0-2% for luminal A, 6-10% for luminal B, and 20-30% for triple negative.

## REFERENCES

- Jordan MA et al. The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. *Mol Cancer Ther* 2005;4(7):1086-1095.
- Cortés J 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(9769):914-923.
- Mauri D. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst* 2005;97(3):188-194.
- Sorlie T et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* 2001;98(19):10869-10874.
- Parker JS et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. *J Clin Oncol* 2009;27(8):1160-1167.

## ACCRUAL

Two hundred patients are planned in 29 sites across in Spain, Germany, Portugal, and France. At least 100 triple-negative breast cancer cases will be included.

Recruitment started in August 2012, with 15 participating patients as of November 2012.

For more information, go to ClinicalTrials.gov (NCT01669252).

## ACKNOWLEDGEMENTS

The trial is funded by a grant from Eisai.

San Antonio Breast Cancer Symposium–December 6-10, 2012.  
This presentation is the intellectual property of the author/presenter.  
Contact Dr. Aleix Prat for permission to reprint and/or distribute.