A TWO-STAGE SIMON DESIGN PHASE II STUDY FOR NON-BRCA METASTATIC BREAST CANCER (MBC) PATIENTS WITH HOMOLOGOUS RECOMBINATION DEFICIENCY TREATED WITH OLAPARIB SINGLE AGENT. (NOBROLA STUDY)

Elena Aguirre[1,2], Kepa Amillano[3], Lourdes Calvo[4], Alfonso Cortés[5], María José Juan[6], Antonia Márquez[7], Manuel Ruiz[8], Sonia Servitja[9], Ander Urrutikoetxea[10], Antonio Llombart[1,11], José Pérez[1], Javier Cortes[1, 5]

[1]MedSIR (Medica Scientia Innovation Research), Barcelona, Spain [2]Hospital Universitario Miguel Servet, Zaragoza, Spain [3]Hospital Sant Joan de Reus, Reus, Spain [4]Complejo Hospitalario Universitario de A Coruña, A Coruña, Spain [5]Hospital Universitario Ramón y Cajal, Madrid, Spain [6]Insituto Valenciano de Oncología, Valencia, Spain [7]Hospital Universitario Virgen de la Victoria, Málaga, Spain [8]Hospital Universitario Virgen del Rocío, Sevilla, Spain [9]Hospital del Mar, Barcelona, Spain [10]Onkologikoa, Donosti, Spain [11] Hospital Arnau Vilanova, Valencia, Spain

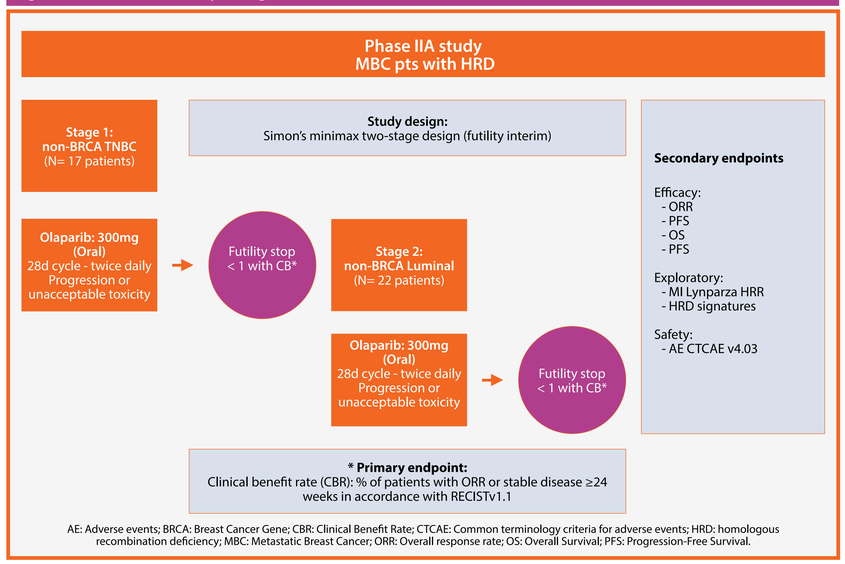
BACKGROUND

- Olaparib is a well-tolerated oral PARP inhibitor [(1)].
- Based on Olaparib monotherapy significant benefit over standard therapy in OlympiaD phase III trial[(2)], FDA approves Olaparib as new standard of care in patients with germline BRCA-positive, HER2-negative metastatic breast cancer who have previously received chemotherapy.
- The aim of this trial is to evaluate the efficacy of olaparib as single agent in non-BRCA MBC patients whose tumors exhibit an homologous recombination deficiency (HRD) signature.

TRIAL DESIGN

- This is an open label, non-randomized, multicenter two-stage phase IIA clinical trial (**Figure 1**).
- Patients will receive oral olaparib 300 mg twice a day during 28 days cycles until progression or unacceptable toxicity.
- HRD signature will be evaluated with tissue-based test: Foundation Medicine, Inc. (FMI) Lynparza Homologous Recombination Repair (HRR) (**Figure 2**).
- Principal eligibility criteria are reported in **Table 1.**

Figure 1. NOBROLA study design



AE: Adverse events; BRCA: Breast Cancer Gene; CBR: Clinical Benefit Rate; CTCAE: Common terminology criteria for adverse events; HRD: homologous recombination deficiency; MBC: Metastatic Breast Cancer; ORR: Overall response rate; OS: Overall Survival; PFS: Progression-Free Survival.

Figure 2. Lynparza mutation test in a panel of 15 HRR pathway genes

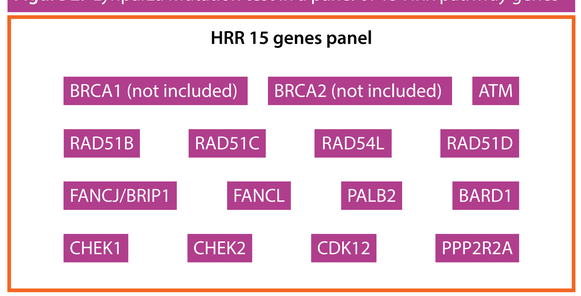


Table 1. Key eligibility criteria for the NOBROLA study

A) INCLUSION CRITERIA:	B) EXCLUSION CRITERIA:
Stage I principal selection criteria are:	
1. Female, age ≥ 18 years.	1. LA breast cancer candidate for a radical treatment.
2. Confirmed non-BRCA with HRD signature patients*.	2. Symptomatic or uncontrolled brain metastases.
3. Triple negative locally advance (LA) or MBC patients.	3. Symptomatic visceral disease.
4. One to three previous lines for the MBC and prior taxanes exposure.	4. Other malignancy ≤ 5 years.
5. RECIST v1.1 evaluable disease.	5. Systematic therapy or radiotherapy ≤ 3 weeks.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.	6. Previous treatment with PARP inhibitors.
7. Adequate bone marrow and organ function.	7. Severe and/or uncontrolled medical condition that contraindicate her participation.
8. Adequate bone marrow and organ function.	
Stage II, The study will be extended to patients with:	
1. Luminal subtype (RH-positive and HER2-negative) LA or MBC patients.	

PRIMARY OBJECTIVE

- To evaluate the efficacy of olaparib monotherapy.

PRIMARY ENDPOINT:

CBR is defined as the percentage of patient's who achieve as best response:

- complete response (disappearance of all target lesions),
- partial response (≥30% decrease in the sum of the longest diameter of target lesions),
- or stable disease ≥24 weeks based on RECIST v.1.1.

SAMPLE SIZE

- Expected accrual will be 39 patients:
  - Simon's minimax two-stage design based on excluding a CBR ≤5% while targeting an improvement of the CBR to ≥20%.
  - 1st stage: 17 evaluable pts (futility stop ≤1 patient with clinical benefit).
  - Final analysis: 35 evaluable pts (positive finding ≥5 pts with clinical benefit).
  - Total accrual 39 pts with 10% drop-out rate correction.
  - Primary analysis will report percentage of pts with clinical benefit and the p-value based on uniformly minimum variance unbiased estimator (UMVUE).
  - Expected sample size to attain 80% power at nominal level of one-sided alpha of 0.05.

  Expected number of non-BRCA patients screened with HRD signature:
  - 128 pts (48 in the first stage; 80 in the second stage).
  - 40% of screened TNBC pts.
  - 25% of luminal (RH-positive and HER2-negative) pts.

SECONDARY OBJECTIVES

- The secondary objectives include efficacy endpoints:
  - ORR: percentage of pts with complete or partial response as best response, in accordance with RECISTv1.1.
  - PFS: Time from the first dose of treatment until objective tumor progression or death by any cause.
  - OS: Time from the first dose of treatment until death by any cause.

EXPLORATORY OBJECTIVES

- HRD signature validity to predict CBR and ORR

SAFETY-RELATED ENDPOINTS

- Adverse events assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

BIBLIOGRAPHY

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Trial registration: NCT03367689 Date of registration: December 11th 2017 First patient included: Not yet recruiting