**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)**

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**BACKGROUND**

- Olaparib is a well-tolerated oral PARP inhibitor (2).
- Based on Olaparib monotherapy significant benefit over standard therapy in Olympiad phase II trial (3). 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 a homologous recombination deficiency (HRD) signature.

**TRIAL DESIGN**

- This is an open label, non-randomized, multicenter two-stage phase II A 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) signature (Figure 2).
- Principal eligibility criteria are reported in Table 1.

**Figure 1. NOBROLA study design**

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

**Table 1. Key eligibility criteria for the NOBROLA study**

<table>
<thead>
<tr>
<th><strong>A) INCLUSION CRITERIA:</strong></th>
<th><strong>B) EXCLUSION CRITERIA:</strong></th>
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<tbody>
<tr>
<td>1. Female, age ≥ 18 years.</td>
<td>1. Luminal subtype (RH-positive and HER2-negative) LA or MBC patients.</td>
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<td>2. Confirmed non-BRCA with HRD signature patients*</td>
<td>1. Previous treatment with PARP inhibitors.</td>
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<td>3. Triple negative locally advance LA or MBC patients.</td>
<td>2. Confirmed non-BRCA with HRD signature:</td>
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<td>4. One to three previous lines for the MBC and prior taxanes exposure.</td>
<td>(N=22 patients)</td>
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<td>5. RECIST v1.1 evaluable disease.</td>
<td>Safety: AE CTCAE v4.03</td>
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<td>6. Eastern Cooperative Oncology Group (ECOG) performance status of 0.1.</td>
<td>(x) finding ≥5 with CTCAE v4.03</td>
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<tr>
<td>7. Adequate bone marrow and organ function.</td>
<td>(x) finding ≤1 with CTCAE v4.03</td>
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**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 v1.1.

**SAMPLE SIZE**

- Expected accrual will be 39 patients: 1. Simon’s minimax two-stage design based on excluding a CBR ≤50% while targeting an improvement of the CBR to ≥20%.

**EXPECTED SAMPLE SIZE**

- 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 connection.

- Primary analysis will report percentage of pts with clinical benefit and the p-value based on uniformly minimum variance unbiased estimator (UMVUE).
- Expected sample to attain 80% power at nominal level of one-sided alpha of 0.05.
- Expected number of non-BRCA patient 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.

**EXPLORATORY OBJECTIVES**

- The secondary objectives include efficacy endpoints:

  - ORR: percentage of pts with complete or partial response as best response, in accordance with RECIST v1.1.
  - 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.

**SAFETY-RELATED ENDPOINTS**

- Adverse events assessed using the National Cancer Institute CTCAE v4.03.

**BIBLIOGRAPHY**


**ACKNOWLEDGEMENT**

We thank all participating patients and study team involved in NOBROLA as well as ASTRAZENECA for their outstanding collaboration and support.

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