MULTICENTER OPEN-LABEL, PHASE II TRIAL, TO EVALUATE THE EFFICACY AND SAFETY OF LIPOSOMAL IRINOTECAN (nal-IRI) FOR PROGRESSING BRAIN METASTASES IN PATIENTS WITH HER2-NEGATIVE BREAST CANCER (THE PHENOMENAL STUDY)

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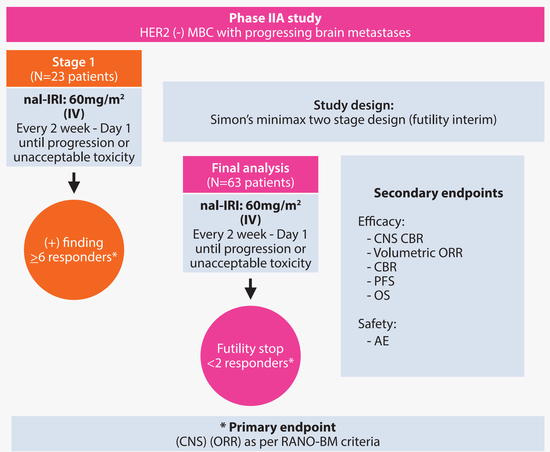
BACKGROUND:

- HER2-negative metastatic breast cancer (MBC) patients with central nervous system (CNS) involvement previously treated with a local therapy had very few possibilities of disease response with conventional systemic treatments (1,2).
- Liposomal irinotecan (nal-IRI) is a novel formulation of irinotecan. It has shown promising activity in patients with CNS involvement (2).
- The aim of this trial is to evaluate the efficacy of nal-IRI as single agent in HER2-negative MBC patients with CNS progression following local treatment with surgery, stereotactic radiosurgery (SRS) or whole-brain radiotherapy (WBRT).

TRIAL DESIGN

- This is an open label, non-randomized, multicenter two-stage phase IIA clinical trial.
- Patients will receive intravenous nal-IRI in a fixed dose of 60 mg/m^2 expressed as irinotecan hydrochloride trihydrate salt on day 1 of a 14-day cycle until progression or unacceptable toxicity (**Figure 1**).
- Principal eligibility criteria are reported in **Table 1**.

Figure 1. PHENOMENAL study design



AE: Adverse events; CBR: Clinical Benefit Rate; CNS: Central nervous system; IV: Intravenous; nal-IRI: liposomal irinotecan; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-Free Survival.

Table 1. Key eligibility criteria for the PHENOMENAL study

Inclusion Criteria:	Exclusion Criteria:
1. Female or male pts age ≥ 18 years.	1. Prior treatment with nal-IRI or any other form of irinotecan.
2. HER2-negative MBC with CNS involvement.	2. Prior anti-cancer therapy within 3 weeks prior to starting study treatment.* *6-weeks for nitrosoureas and mitomycin-C.
3. ≥1 brain lesion according to RECIST v1.1.	3. Radiation therapy encompassing > 30% of bone marrow.
4. Prior local treatment with surgery and/or SRS and/or WBRT.	4. Significant chronic gastrointestinal disorder.
5. Pretreated with taxanes.	5. Baseline clinically relevant toxic effects of any prior anticancer therapy.
6. ≥1 prior chemotherapy for advance disease.	6. Other malignancy ≤ 5 years.
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤1.	7. Clinically significant cardiovascular disease (NYHA Class III or IV).
8. Adequate bone marrow and organ function.	8. Active infection or an unexplained fever >38.5°C.
	9. Severe and/or uncontrolled medical condition that contraindicate pts' participation.

PRIMARY OBJECTIVE:

- To assess the efficacy of nal-IRI in patients as determined by the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria.

PRIMARY ENDPOINT:

CNS ORR per the RANO-BM criteria, defined as proportion of patients who experienced:

- Complete response (CR): disappearance of all CNS target lesions sustained ≥ 4 weeks (no new lesions, no corticosteroids, stable or improved clinically).
- Partial response (PR): decreased ≥30% from baseline in the sum longest diameter of CNS target lesions sustained ≥ 4 weeks (no new lesions, no corticosteroids, stable or improved clinically).

SAMPLE SIZE:

- Expected accrual will be 63 patients:
  - Simon's minimax two-stage design based on excluding a CNS ORR ≤5% while targeting an improvement of the CNS ORR to ≥15%.
  - 23 evaluable patients for the first stage (futility stop ≤1 responders).
  - 56 evaluable patients for the final analysis (positive finding ≥6 responders).
  - Total accrual 63 patients with 10% drop-out rate correction.
  - Primary analysis will report percentage of responders 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.

SECONDARY OBJECTIVES:

- The secondary objectives include efficacy endpoints:
  - CNS CBR: number of patients with CR, PR or stable disease [SD] ≥12 weeks by the number of patients analyzed.
  - ORR according to a CNS volumetric parameter: number of patients with CR, PR or >65% reduction of CNS lesion by the number of patients analyzed.
  - CBR per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1: number of patients with CR, PR and SD ≥24 weeks by the number of patients analyzed.
  - 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 outcomes:
  - Adverse events (AE) assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

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Trial registration: NCT03328884. Date of registration: November 1st, 2017. First patient included: July 05th, 2017.