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Effectiveness of olaparib plus trastuzumab in patients with HER2-positive, germinal *BRCA*–mutated or Homologous Recombination Deficient advanced breast cancer. The OPHELIA Study.

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BACKGROUND

- In the OlympiAD trial the use of poly(adenosine diphosphate–ribose) polymerase inhibitor (PARPi) olaparib (Lynparza®) resulted in better progression–free survival (PFS) than standard chemotherapy, which led to approval in patients (pts) with Human Epidermal Growth Factor Receptor 2 (HER2)-negative, germline *BRCA1*- and/or *BRCA2*-mutated (gBRCAm) metastatic breast cancer [1].
- There is a potential therapeutic role for PARPis in pts with defective DNA repair [2]. Limited data from case series of pts with HER2-positive (HER2[+]) advanced breast cancer (ABC) showed that BRCA1 and BRCA2 gene mutation carriers account for 2.1-10% and 6.8-13%, respectively [3-4]. Tumors with high Homologous Recombination Deficiency (HRD) score are known to have a high sensitivity to platinum-based chemotherapy as well as PARP inhibitors. Although in the TCGA dataset HRD was confirmed in about 3% of HER2[+] tumors, recent studies estimated genomic HRD at 9-27%[5-6].
- Preclinical data support a strong synergism between olaparib (Lynparza®) and trastuzumab in HER2[+] cells that are sensitive to PARPis [7].
- This study will evaluate the efficacy and safety of olaparib (Lynparza®) plus trastuzumab in pts with HER2[+], gBRCAm (Cohort A) or germline *BRCA1*- and/or *BRCA2*-wild-type (gBRCAwt) /HRD (Cohort B) ABC.

OBJECTIVES

- **PRIMARY OBJECTIVE**

To assess the efficacy –as determined by the overall response rate (ORR) and PFS based on Response evaluation criteria in solid tumors (RECIST) v.1.1– of olaparib (Lynparza®) in combination with trastuzumab in pts with HER2[+], gBRCAm ABC (Cohort A).

- **CO-PRIMARY ENDPOINTS**
  - ORR is defined as the percentage of pts with complete response (CR) or partial response (PR) confirmed at least 4 weeks after the initial response assessment.
  - PFS is defined as the time from treatment initiation to the date of the first documented progressive disease or death due to any cause, whichever occurs first.

- **SECONDARY OBJECTIVES**
  - To assess the efficacy –as determined by the clinical benefit rate (CBR), duration of response (DoR), maximum tumor reduction and overall survival (OS)– of olaparib (Lynparza®) in combination with trastuzumab in pts with HER2[+], gBRCAm ABC (Cohort A).
  - To assess the efficacy –as determined by the ORR, PFS, CBR, DoR, maximum tumor reduction, and OS– of olaparib (Lynparza®) in combination with trastuzumab in pts with HER2[+], gBRCAwt / HRD ABC (Cohort B)
  - To evaluate health-related quality of life (HRQoL) measured by the European Organization for Research and Treatment of Cancer (EORTC) and EuroQoL 5D (EQ-5D) questionnaires both in Cohort A and Cohort B.

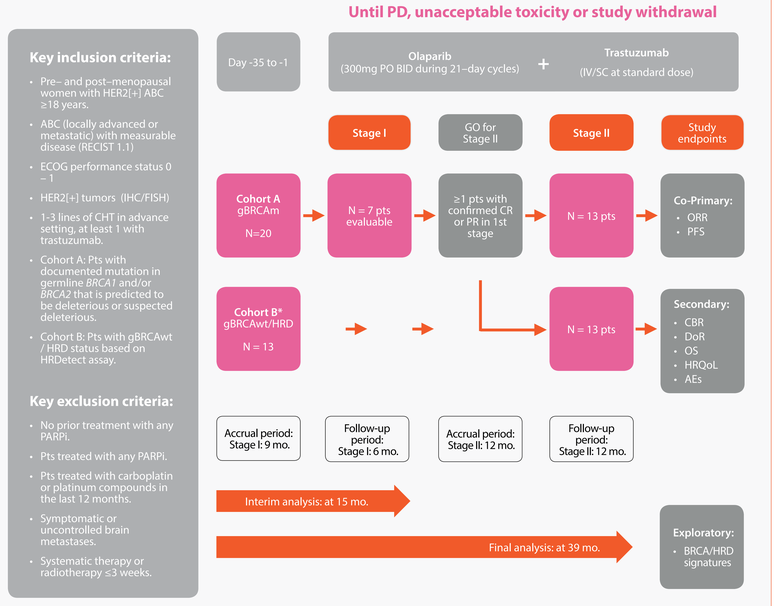
- **SAFETY OBJECTIVES**
  - To assess adverse events using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

- **EXPLORATORY OBJECTIVES**
  - To assess prevalence and predictive value of both genomic profiles (mutations in germline *BRCA1* and/or *BRCA2* genes and gBRCAwt / HRD status) in HER2[+] ABC pts.
  - To investigate new molecular markers that are predictive of response and/or resistance to olaparib (Lynparza®) in combination with trastuzumab.

TRIAL DESIGN

- This is a multicenter, single–arm, two–cohort, Simon's two–stage, phase II trial.
- The cohort A will recruit N=20 gBRCAm ABC pts. The cohort B will recruit N=13 gBRCAwt / HRD ABC pts that will require prospective central testing of both tumor tissue and blood samples according to the whole genome sequencing (WGS)-based HRDetect predictor at the Wellcome Trust Sanger Institute [8].
- Pts will receive olaparib (Lynparza®) tablets (300mg taken oral twice daily during 21–day cycles) in combination with trastuzumab (intravenous or subcutaneous at standard dose) until progression or unacceptable toxicity.

OPHELIA Study Design



ABC: Advance breast cancer; AEs: Adverse events; BID: Twice daily administration; CBR: Clinical benefit rate; CHT: Chemotherapy; CR: Complete response; DoR: Duration of response; ECOG: Eastern Cooperative Oncology Group; FISH: Fluorescence in situ hybridization; gBRCAm: germline *BRCA1*- and/or *BRCA2*-mutated; HER2[+]: Human Epidermal Growth Factor Receptor 2-positive; HRD: Homologous Recombination Deficient; HRQoL: Health-related quality of life; IHC: Immunohistochemistry; mo.: Months; IV: Intravenous; ORR: Overall response rate; PARPi: Poly(adenosine diphosphate–ribose) polymerase inhibitor; PD: Progressive disease; PFS: Progression-free survival; PO: Per os, orally; PR: Partial response; pts: Patients; RECIST: Response evaluation criteria in solid tumors; SC: Subcutaneous.

* **gBRCA / HRD** status: Prospective central testing of both tumor tissue and blood samples according to the whole genome sequencing-based HRDetect predictor at the Wellcome Trust Sanger Institute [8].

- **SAMPLE SIZE**

· Cohort A

We plan a Simon's minimax two–stage design, with 7 pts in stage I and, if ≥1 responding pts, additional 13 pts in stage II.

First co-primary endpoint (ORR):

Final ORR will be promising with ≥4 responders among 18 evaluable pts (H0: ORR≤5%; HA: ORR≥30%). These give us an 80% power at 0.025 one–sided alpha level. We will accrual 20 pts to account a 10% drop-out rate correction.

Second co-primary endpoint (PFS):

PFS estimation in Cohort A will be based a one–arm log–rank test (H0: PFS≤3–months; HA: PFS≥6–months). These give us an 80% power at 0.025 one–sided alpha level.

· Exploratory Cohort B

Additional 13 pts in stage II will be recruited according to a binomial one-stage design.

Final ORR will be promising with ≥3 responders among 13 pts ($p<0.025$; H0: ORR≤5%).

TRIAL ENROLLMENT

The **OPHELIA trial** is open and actively accruing at 17 Spanish institutions.

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

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Trial registration: NCT03931551. **Date of registration:** April 30, 2019. **First patient included:** August 7, 2019.