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Effectiveness of Niraparib plus Aromatase Inhibitors (AI) for germinal *BRCA1/2*-mutated (g*BRCA*m) or Homologous Recombination Deficient (HRD), Hormone Receptor (HR)+/Human Epidermal Growth Factor Receptor 2 (HER2) Advanced Breast Cancer (ABC). The LUZERN Strategy

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BACKGROUND

- Poly(ADP-ribose)polymerase (PARP) inhibition is a novel approach leading to cell death through synthetic lethality in tumor cells with deficiencies in DNA-repair mechanisms and patterns of genomic instability. [1]
- Niraparib (ZEJULA®) is a potent, orally active, and well-tolerated PARP1/2 inhibitor which have demonstrated clinical activity in patients (pts) with advanced ovarian [2-4] and breast [5] cancers. A phase III trial is exploring niraparib as second-line treatment in pts with g*BRCA*m, HER2[-] ABC. [6]
- Tumor mutations in *BRCA1* and *BRCA2* are estimated to be present in 20% to 25% of pts with triple-negative breast cancer [1,7], while about 5% of HR[+]/HER2[-] breast cancer pts harbor g*BRCA*m and 10% to 20% approximately are HRD. [8,9]
- This study will evaluate the efficacy and safety of niraparib combined with AI in pts with pretreated g*BRCA*m or HRD, HR[+]/HER2[-] ABC.

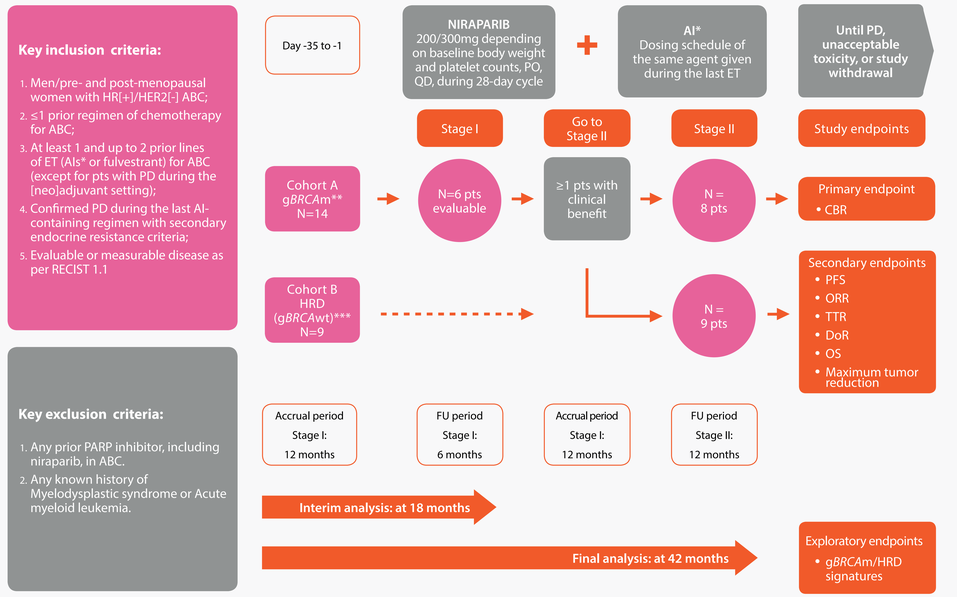
OBJECTIVES

- **PRIMARY OBJECTIVE**
  - To assess the efficacy –as determined by the clinical benefit rate (CBR)– of niraparib in combination with AIs in unresectable locally advanced or metastatic HR[+]/HER2[-] breast cancer pts harboring either g*BRCA*m or HRD (g*BRCA*wt).
- **PRIMARY ENDPOINT**
  - CBR, defined as the percentage of pts who experience a complete response (CR), partial response (PR), or stable disease (SD) for at least 24 weeks as locally assessed using Response Evaluation Criteria in solid Tumors (RECIST) 1.1.
- **SECONDARY OBJECTIVES**
  - To assess the efficacy –as determined by the progression-free survival (PFS), objective response rate (ORR), time to response (TTR), duration of response (DoR), overall survival (OS), and maximum tumor reduction– of niraparib plus AIs in these pts.
  - To evaluate the safety and tolerability of niraparib plus AIs in these pts.
- **SECONDARY ENDPOINTS**
  - PFS, ORR, TTR, DoR, and maximum tumor reduction as locally assessed using RECIST 1.1.
  - Incidence of adverse events (AEs), prespecified AEs, change from baseline in targeted vital signs, and change from baseline in targeted clinical laboratory test results according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) 5.0.
- **EXPLORATORY OBJECTIVES**
  - To assess prevalence and predictive value of g*BRCA*m and HRD in these pts.
  - To investigate new molecular markers that are predictive of response and/or resistance to niraparib combined with AI in these pts.

TRIAL DESIGN

- This is a multicenter, open-label, single-arm, two-cohort, Simon's two-stage, phase II trial.
- The cohort A will recruit g*BRCA*m, HR[+]/HER2[-] ABC pts. The exploratory cohort B will enroll HRD (g*BRCA*wt), HR[+]/HER2[-] ABC pts if the criterion of the cohort A for continuing to the stage II is met.
- Pts will receive niraparib (200 or 300 mg depending on baseline body weight and platelet counts, orally, once a day, during 28-day cycle) plus the same AI administered during the last endocrine therapy until progressive disease, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.

LUZERN STUDY DESIGN



* For pre-menopausal and male patients, luteinizing hormone-releasing hormone (LHRH) analogs are required.

** Cohort A: Pts with documented g*BRCA*m that is predicted to be deleterious or suspected deleterious.

*** Cohort B: Pts with HRD status *(gBRCAwt)* based on Myriad myChoice HRD Plus test.

Abbreviations
ABC: Advanced breast cancer; AI: Aromatase inhibitor; **CBR:** Clinical benefit rate; **DoR:** Duration of response; **ET:** Endocrine therapy; **FU:** Follow up; **gBRCAm:** germinal mutation in *BRCA1/2*; **gBRCAwt:** germinal *BRCA1/2* wild type; HR: Hormone receptor; **HRD:** Homologous recombination deficient; **HER2:** Human epidermal growth factor receptor 2; **ORR:** Objective response rate; **OS:** Overall survival; **PARP:** Poly(ADP-ribose)polymerase; **PD:** Progressive disease; **PFS:** Progression-free survival; **PO:** orally; Pts: Patients; **QD:** Once a day; **RECSIT:** Response evaluation criteria in solid tumors; **TTR:** Time to response.

SAMPLE SIZE

- **Cohort A**
  - The trial uses a Simon's two-stage minimax design. If ≥1 out of the first 6 pts of the cohort A achieve clinical benefit (CB), 8 additional pts will be recruited during stage II. At least 3 out of 12 evaluable pts with CB will be adequate to justify this strategy in further studies. Considering a drop-out rate of 10%, 14 pts will be needed to attain 80% power at nominal level of one-sided alpha of 0.025.
- **Exploratory Cohort B**
  - The exploratory cohort B will be initiated if the criterion of the cohort A for continuing to the stage II is met.

TRIAL ENROLLMENT

The **LUZERN trial** is active for enrolment.

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

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Trial registration: NCT04240106. Date of registration: January 27, 2020.