Phase II study evaluating the addition of elacestrant to niraparib compared to niraparib alone in patients with HR+/HER2- locally advanced or metastatic breast cancer with germline or tumor BRCA1/2 and/or PALB2 mutations – ELEMENT

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P 097

Background

Elacestrant, a selective estrogen receptor degrader (SERD), proved safe and effective in heavily pretreated patients with hormone receptor-positive (HR+), human epidermal growth factor-2 negative (HER2-) metastatic BC (mBC) who received prior treatment with endocrine therapy (ET)[1].

Niraparib is a poly-adenosine diphosphate ribose polymerase (PARP) inhibitor that has demonstrated efficacy in patients with platinum-sensitive, recurrent ovarian cancer, regardless of the presence or absence of germline *BRCA1/2* (g*BRCA1/2)* mutations, with moderate bone marrow toxicity[2], and shown activity in patients with g*BRCA* mutated, HER2-negative locally advanced or mBC, previously treated with ≤2 prior lines of chemotherapy[3].

The purpose of this study is to investigate the efficacy and safety of adding elacestrant to niraparib compared to niraparib alone in patients with HR+/HER2- locally advanced or mBC harboring a *BRCA1/2* or *PALB2* (germline/tumor) mutation.

Study design

ELEMENT (GBG114; EU-CT: 2023-504925-38) is a phase II, prospective, multi-center, randomized, open label, parallel group study in patients with HR-positive, HER2-negative locally advanced or mBC with g/t*BRCA1/2* or g/t*PALB2* mutation, with 2:1 randomization to arm A (niraparib + elacestrant) or arm B (niraparib).

Study objectives

Primary objective:

To evaluate the impact on progression free survival (PFS) of elacestrant with niraparib compared to niraparib alone in patients with HR+/HER2- locally advanced or mBC harboring a g/t*BRCA1/2* or g/t*PALB2* mutation.

Secondary objectives:

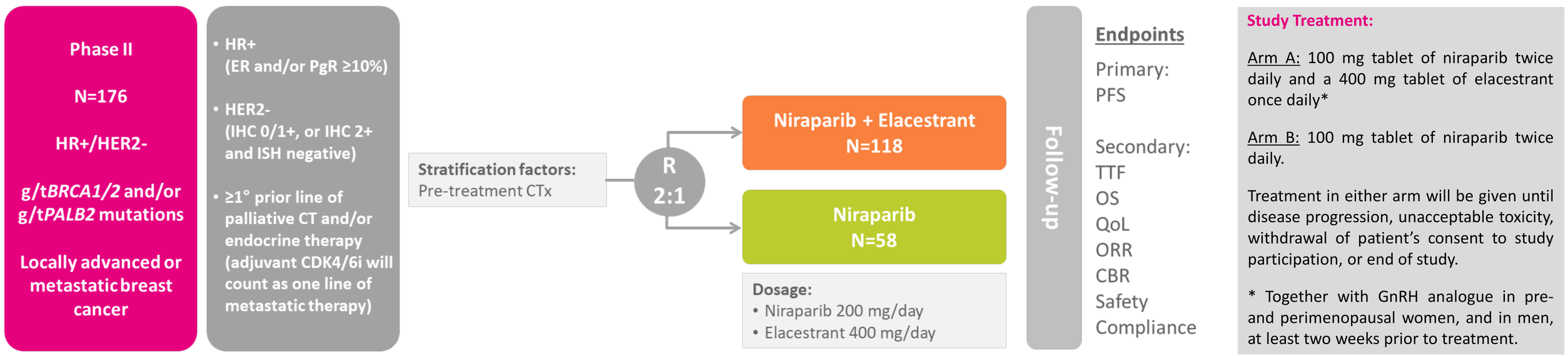
- To compare time-to-treatment failure (TTF)
- To compare overall survival (OS)
- To assess and compare patient reported outcome (PRO) and quality of life (QoL)
- To compare PFS, TTF and OS in the stratified subgroups (pre-treatment palliative chemotherapy yes vs. no and exploratory subgroups (prior fulvestrant therapy; *ESR1* wild type (or not done) vs. mutant; *BRCA1/2* mutant vs. *PALB2* mutant)
- To compare overall response rate (ORR)
- To compare the clinical benefit rate (CBR)
- To assess and compare safety
- To assess and compare compliance

Translational research objectives:

- To assess *BRCA1/2*, *PALB2*, and *ESR1* mutation status via liquid biopsy
- To assess ctDNA at baseline, during treatment and at disease progression
- To explore ctDNA dynamics as early predictors of disease progression in ctDNA positive patients.
- To explore the predictive value of markers for elacestrant and niraparib treatment
- To explore markers for resistance to elacestrant and niraparib therapy.

Other research objectives:

To assess pharmacokinetics (PK) of the combination and potential PK drug-drug interactions in a subset of patients.



Key Inclusion Criteria

- Age ≥ 18 years
- Centrally confirmed locally advanced HR+/HER2- mBC according to ASCO/CAP guidelines
- Patients with deleterious or suspected deleterious g/t*BRCA1/2* and/or g/t*PALB2* mutations
- Females or male patients, who received at least one prior line of chemotherapy or endocrine-based therapy for irresectable, locally advanced, or metastatic disease, or patients with recurrent, unresectable, locally advanced, or metastatic disease after adjuvant treatment with CDK4/6 inhibitor therapy.
- Willingness and ability to provide archived formalin fixed paraffin embedded tissue (FFPE) block or a partial block from archived tumor or metastasis
- Life-expectancy > 6 months

Key Exclusion Criteria

- Known hypersensitivity reaction to one of the substances used in the study
- Active or newly diagnosed CNS metastases, including leptomeningeal carcinomatosis, carcinomatous meningitis, or radiographic signs of CNS hemorrhage. Note: Patients with stable brain metastases are eligible.
- Presence of symptomatic metastatic visceral disease at risk of life-threatening complications in the short term
- Inadequate organ function prior to enrolment
- Existing contraindication against the use of the elacestrant or niraparib
- Prior treatment with PARP inhibitors

Collection of Biomaterial

Study requirements	Screening phase	Treatment Phase		
	Before randomization	Pre-treatment	During treatment	At progression
FFPE tissue breast tumor	X			X (if available)
Plasma liquid biopsy (ctDNA)		X	Day 15, thereafter every 90 days	X and EOT
Whole blood (Pharmacogenetics)		X		

Follow-Up

Follow-up data (including first new therapy, subsequent disease progression data, and death) will be collected every 3 months until progression or end of study, whatever occurs first. After progression, data will be collected every six months until end of study.

Recruitment

- The ELEMENT study will be conducted in approximately 40 sites across Germany
- First patient in Q2/2024, last patient Q2/2027, final analysis Q2/2028

Disclosure Statement

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1. Bardia et al., J Clin Oncol 2021; **2.**; Mirza MR et al., N Engl J Med 2016; **3.** Turner et al., Clin Cancer Res 2021

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