Phase II neoadjuvant study evaluating capivasertib plus fulvestrant vs fulvestrant in patients with primary high-risk lobular breast cancer - LOBSTER

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Background

- 15% of breast cancers (BC) have an invasive lobular cancer (ILC), posing challenges such as larger size, increased nodal involvement, distinct genomic features (*CDH1* mutations, PI3K/AKT/mTOR alterations), and reduced response to standard neoadjuvant chemotherapy[1,2].
- Neoadjuvant trials explored endocrine therapy +/- cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) achieving complete cell cycle arrest (CCCA) in up to 90%. The CAPItello-291 trial showed an improved progression-free survival with fulvestrant plus capivasertib vs. fulvestrant alone in HR+/HER2− pretreated advanced BC[3].
- However, the lack of studies focusing on ILC highlights the need for tailored approaches to possibly replace unnecessary chemotherapy in this subtype.

Study design

LOBSTER (GBG118; EUCT: 2023-509292-17-00) is a multicenter, prospective, open-label, randomized phase II trial comparing capivasertib plus fulvestrant with fulvestrant alone for 10 weeks as neoadjuvant treatment for primary high-risk lobular BC patients.

Study overview and objectives

Overview:

LOBSTER will evaluate the CCCA rate assessed by Ki67 drop below ≤2.7% with capivasertib in combination with fulvestrant compared with fulvestrant alone as neoadjuvant treatment for patients with high-risk primary lobular BC. The study will enroll and randomize 120 patients equally into the two treatment groups.

Primary objectives

- To assess CCCA, defined as a Ki67 drop to ≤2.7% after approximately 10 weeks, the collected biomaterial will be analyzed centrally.

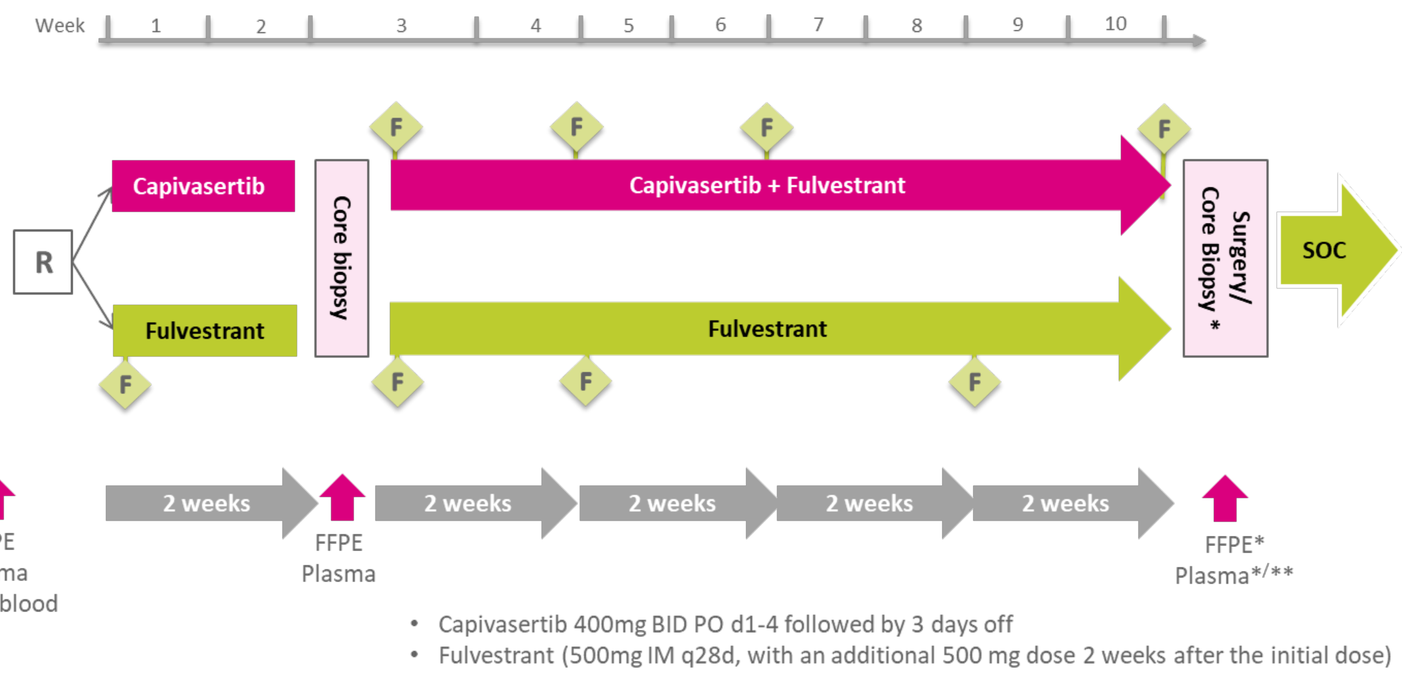
Secondary objectives

- To assess safety and tolerability
- To assess breast conservation rate (BCS)
- To assess pathological complete response rate (pCR) by different definitions
- To assess invasive disease-free survival (iDFS) and overall survival (OS) by referring to data from GBG patient's patient self-reporting registry (PSR)

Translational objectives

- To assess treatment effect by AKT pathway alteration
- To assess CCCA after 2 weeks
- To evaluate changes in gene expression profile and proteomics after window phase
- To assess ER and PgR downregulation, changes in TILs and changes in *FOXO3A* expression
- To assess rates of mutations by next-generation sequencing (NGS)

N=120 invasive, early BC
- Centrally confirmed:
  - Lobular histology
  - HR+ (ER/PR≥10%)/HER2-
- Stage: >cT1c and cN+ or >cT2 any cN
- Postmenopausal
- Ki67 >10%



Follow Up PSR

Primary endpoint:
CCCA rate (Ki67 ≤2.7%) after 10 weeks
Secondary endpoint:
- Safety and tolerability
- BCS rate
- pCR
- iDFS and OS (within GBG self-reporting registry)

* within 4 weeks after last fulvestrant, but prior to any new cancer treatment ** before surgery

Key Inclusion Criteria

- Postmenopausal women with age at diagnosis ≥ 18 years
- Centrally confirmed untreated ILC
- HR+ (ER/PR≥10%), HER2- (IHC 0-1+ or ISH negative)
- High risk of recurrence: cT1c and nodal involvement or ≥cT2 (irrespective of nodal involvement)
- Ki67 > 10%
- No clinical evidence of distant metastatic disease
- HbA1c <8.0% (63.9 mmol/mol)

Key Exclusion Criteria

- Female patients of childbearing potential
- Excisional biopsy or lumpectomy performed prior to study entry
- Surgical axillary staging procedure prior to randomization (FNA or core biopsy allowed)
- Any previous treatment including endocrine therapy, chemotherapy, radiotherapy, or targeted therapy for the currently diagnosed BC
- History of type I or type II diabetes mellitus requiring insulin
- Severe and relevant comorbidities (e.g. cerebrovascular incident, symptomatic pulmonary embolism, active infection, history of HIV or tuberculosis or hepatitis B)
- History of and/or active cardiac disease that would preclude the use of study treatments

Collection of Biomaterial

Study requirements	Screening phase	Treatment Phase	
	Before randomization	Week 2 (day 15 +/- 3 days)	At End of therapy
FFPE tumor tissue	X[a]	X[b]	X[c]
Whole blood	X		
Plasma (ctDNA)	X	X	X[d]

a: Formalin-fixed, paraffin-embedded (FFPE) tissue from core biopsy of primary breast tumor (central testing and translational research); **b:** FFPE tissue from breast tumor core biopsy after 2 weeks of study treatment, but before first dose of fulvestrant in the capivasertib arm; **c:** FFPE tissue of residual breast tumor (core biopsy or surgical tissue) within 4 weeks after last dose of fulvestrant, but prior to any subsequent anticancer treatment ; **d:** Prior to surgery

Follow-Up

After analysis of the primary endpoint, follow up data on long-term survival will be collected within the GBG patient self-reporting registry (GBG 118) and will be used to assess iDFS, OS and for further translational research analyses.

Recruitment

- The study will be conducted in approximately 30 sites across Germany.
- First patient in Q2/2024; Last patient in Q1/2026; Last patient out Q2/2026

Disclosure Statement

ND, SS and **VN** declares to be GBG Forschungs GmbH employee. GBG Forschungs GmbH received funding for research grants from Abbvie, Amgen, AstraZeneca, BMS, Daiichi-Sankyo, Gilead, Molecular Health, Novartis, Pfizer and Roche (paid to the institution); other (non-financial/medical writing) from Daiichi-Sankyo, Gilead, Novartis, Pfizer, Roche and Seagen (paid to the institution). GBG Forschungs GmbH has licensing feesfrom VMscope GmbH. In addition, GBG Forschungs GmbH has a patent EP21152186.9 pending, a patent EP19808852.8 pending, and a patent EP14153692.0 pending. **AS** reported grants from Celgene, Roche and AbbVie. Personal fees from Cellgene, Roche, Pfizer, AstraZeneca, Novartis, MSD, Tesaro, Lilly, Seagen, Gilead, GSK, Bayer, Amgen, and Pierre Fabre, and travel grants from Celgene, Roche, Pfizer and AstraZeneca. **MU** reports consulting fees to the institution from Astra Zeneca, Daiichi Sankyo, Lilly, MSD Merck,Myriad Genetics, Novartis, Pierre Fabre, Pfizer, Gilead, Roche, Sanofi Aventis, Seagen, Stemline, CD Pharma outside the submitted work as well as honoraria for lectures and presentations to the institution from Astra Zeneca, Daiichi Sankyo, Lilly, Myriad Genetics, Novartis, Pierre Fabre, Pfizer, Roche, Sanofi Aventis, Stemline, all outside the submitted work. **AS** reported grants from Celgene, Roche and AbbVie. Personal fees from Cellgene, Roche, Pfizer, AstraZeneca, Novartis, MSD, Tesaro, Lilly, Seagen, Gilead, GSK, Bayer, Amgen, and Pierre Fabre, and travel grants from Celgene, Roche, Pfizer and AstraZeneca. **JH** reports grants to the institution from DaiichiSankyo, Gilead, Novartis, Pfizer, Roche, Seagen during the conduct of this work as well as grants to the institution from AbbVie, AstraZeneca, BMS, DaiichiSankyo, MolecularHealth, Novartis, Roche, Pfizer outside the submitted work. JH reports personal consulting fees from MSD Oncology, Novartis, Palleos Health Care, Pfizer, Roche Pharma, Seagen outside the submitted work as well as honoraria for lectures and presentations from DaiichiSankyo, Gilead, Novartis, Pfizer, Roche Pharma, Seagen outside the submitted work as well as nonfinancial support from Hologic. JH declares to be GBG Forschungs GmbH employee; GBG Forschungs GmbH has following royalties/patents: EP14153692.0, EP21152186.9, EP15702464.7, EP19808852.8 and VM Scope GmbH. SL reports grants to the institution from AbbVie, AstraZeneca, Celgene, Daiichi-Sankyo, Immunomedics/Gilead, Molecular Health, Novartis, Roche, Pfizer. **SL** declares to be GBG Forschungs GmbH employee; GBG Forschungs GmbH has following royalties/patents: EP14153692.0, EP21152186.9, EP15702464.7, EP19808852.8 and VM Scope GmbH; honoraria for lectures and presentations from AstraZeneca, DSI, Gilead, Pfizer, Novartis, Roche, Seagen, Medscape as well as honoraria for advisory boards from Abbvie, Amgen, AstraZeneca, BMS, Celgene, DSI, EirGenix, Gilead, GSK, Lilly, Novartis, Merck, Olema, Pfizer, Pierre Fabre, Relay Therapeutics, Roche, Seagen. SL reports non-financial interest as advisory role in AGO Kommission Mamma, as principal investigator (Aphinity), as member in AGO, ASCO, DKG, ESMO and other nonfinancial interest from AstraZeneca, Daiichi-Sankyo, immunomedica/Gilead, Novartis, Pfizer, Roche and Seagen. All other authors report no conflict of interest.

References

1. Fernández B et al. J Clin Pathol 2011; **2.** Desmedt C et al. J Clin Oncol 2016. **3.** Turner NC et al. N Engl J Med 2023

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