PREcoopERA Window-of-Opportunity trial of giredestrant +/- triptorelin vs. anastrozole + triptorelin in premenopausal patients with ER-positive/HER2-negative early breast cancer

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Background

Current standard of care for premenopausal women with estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative (ER-positive/HER2-negative) early breast cancer (BC) frequently involves ovarian function suppression (OFS) in addition to endocrine therapy[1]. However, young women may exhibit lower treatment compliance due to OFS toxicity, impacting their quality of life (QoL). While luteinizing hormone releasing hormone (LHRH) agonists are effective as OFS, their injections and side-effects may be unacceptable to some women [2,3]. Giredestrant, a new oral selective ER degrader (SERD) exhibits promise as a potent anti-proliferative agent[4].

PREcoopERA is a 4-week neoadjuvant trial assessing giredestrant's efficacy with and without OFS in premenopausal ER-positive/HER2-negative BC patients.

Study design

PREcoopERA (NCT05896566, GBG 112) is a multicenter, open-label, 2:2:1 randomized window-of-opportunity (WOO) trial. 220 premenopausal women with ER-positive/HER2-negative operable invasive BC will be randomly assigned to receive either giredestrant alone, giredestrant plus triptorelin, or anastrozole plus triptorelin.

Study objectives

Primary objective:

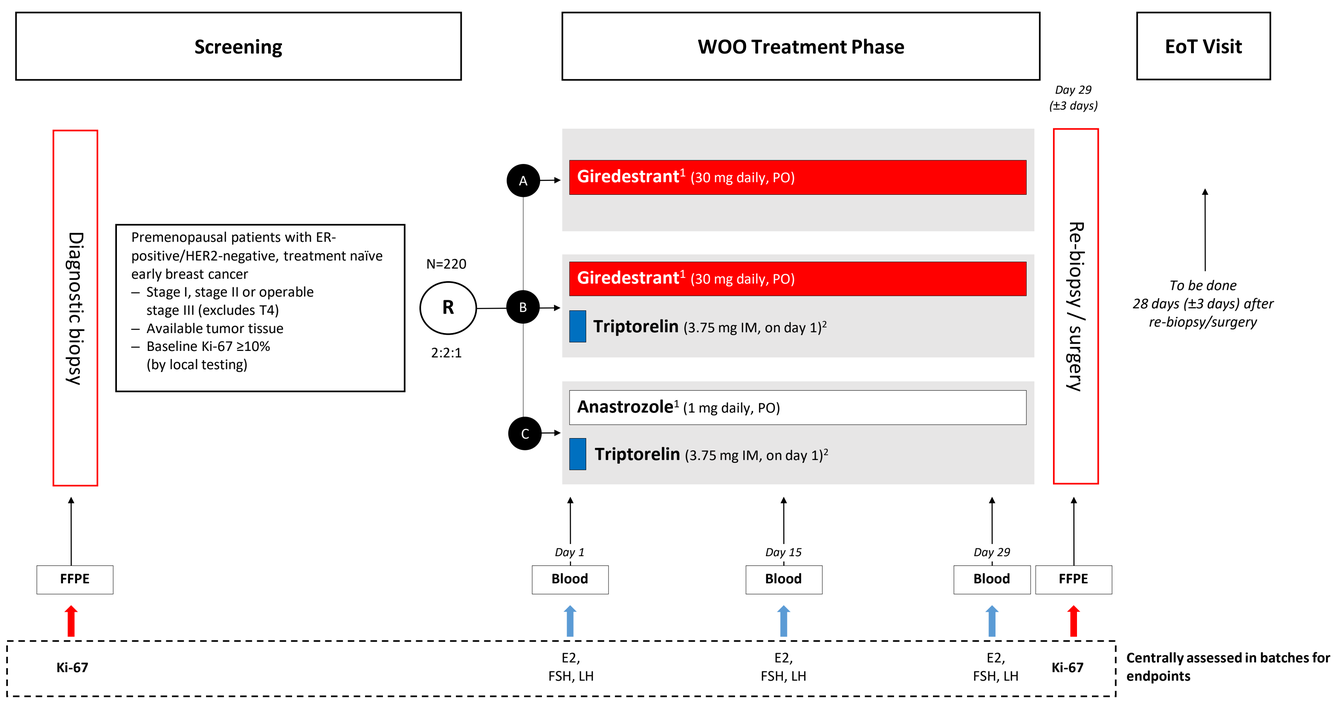
- To determine if 4 weeks of giredestrant + triptorelin provides greater anti-proliferative activity (change in Ki-67) than anastrozole + triptorelin among premenopausal women with ER-positive/HER2-negative BC
- To determine if 4 weeks of giredestrant without triptorelin provides anti-proliferative activity (change in Ki-67) that is similar (non-inferior) to giredestrant + triptorelin among premenopausal women with ER-positive/HER2-negative BC

Secondary objectives:

- To assess if 4 weeks of giredestrant without triptorelin provides greater anti-proliferative activity than anastrozole + triptorelin among premenopausal women with ER-positive/HER2-negative BC
- To assess the safety and tolerability of giredestrant with or without triptorelin over 4 weeks among premenopausal women with ER-positive/HER2-negative BC

Explorative Objectives:

- To assess the reduction of estradiol and other blood-based hormonal levels after 4 weeks of giredestrant with or without triptorelin among premenopausal women with ER-positive/HER2-negative BC
- To assess whether there is heterogeneity of anti-proliferative activity of 4 weeks of giredestrant without triptorelin according to clinical features among premenopausal women with ER-positive/HER2-negative BC.
- To investigate whether 4 weeks of treatment affects changes in tumor tissue and/or circulating biomarkers, for example the gene expression profile, that may provide insight to heterogeneity of treatment activity or early resistance onset in this population.



[1] *Oral treatment (giredestrant or anastrozole) is given from day 1 until the day of re-biopsy/surgery*
[2] *If re-biopsy/surgery cannot be done on day 29 (±3 days) from first injection, a second triptorelin injection should be given on day 29 (±3 days).*

Trial endpoints

Primary endpoint:

Change in Ki-67 between a pre-treatment tumor biopsy and a post-treatment tumor re-biopsy

Secondary endpoints:

- Complete cell cycle arrest (CCCA), defined as Ki-67 ≤2.7% on post-treatment tumor rebiopsy
- Adverse events according to CTCAE v5.0

Key Inclusion Criteria

- Premenopausal women age ≥18 years
- Histologically confirmed, operable invasive breast cancer
- ER-positive (≥1%)/HER2-negative tumor (ASCO/CAP)
- Ki-67 ≥10% in diagnostic biopsy
- Normal hematologic, renal and liver function
- Negative serum or urine beta HCG pregnancy test within 5 weeks prior to randomization
- Availability of pre-treatment tumor biopsy

Key Exclusion Criteria

- Stage IV (metastatic) BC
- Inflammatory BC (cT4d)
- Previous systemic or local treatment
- Received any GnRH/LHRH analog within 12 months of randomization
- Major surgery within 4 weeks of randomization
- Known clinically significant history of liver disease
- History of documented hemorrhagic diathesis, coagulopathy, or thromboembolism
- Active cardiac disease or history of cardiac dysfunction
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias

Collection of Biomaterial

Study requirements	Screening phase	Treatment Phase			Post-treatment
	Before randomization	Day 1	Day 15	Day 29	At surgery
FFPE tissue breast tumor	X				X
Whole blood (Pharmacogen)		X	X	X	

Trial duration

Clinical trial is expected to span approximately 28 months, including a start-up phase of 6 months during which the sites will be activated, 20 months of accrual and 2 months of additional follow-up time after the last patient is enrolled.

Start and end dates

Since the first patient was randomized in February 2024 in Germany, enrollment has reached 5 out of 35 patients, contributing to a steady increase in global recruitment, which currently stands at 15 out of 220.

References

1. Francis, P. A., et al. (2018). NEJM. **2.** Pistilli, B., et al. (2020), J Clin. Oncol. **3.** Ribi, K., et al. (2020). Breast Cancer Res Treat **4.** Liang, J., et al. (2021). J Med Chem.

Disclosure Statement

CD reports grants from European Commission H2020, grants from BMBF; grants from German Cancer Aid Translational Oncology, grants from German Breast Group, during the conduct of the study; personal fees from Novartis, Roche, MSD Oncology, Daiichi Sankyo, Merck, AstraZeneca, Molecular Health, grants from Myriad to the institution, outside the submitted work; In addition, CD has a patent VMscope digital pathology software with royalties paid, a patent WO2020109570A1 - cancer immunotherapy pending, and a patent WO2015114146A1 and WO2010076322A1- therapy response issued. **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. **HN** declares to be GBG employee and 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, Daiichi Sankyo, MolecularHealth, Novartis, Roche, Pfizer outside the submitted work. SR 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, PfizerSL 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.

Presented at: 43. Jahrestagung Deutsche Gesellschaft für Senologie 06.–08. Juni 2024, Dresden

This study is funded by Roche and sponsored by ETOP IBCSG Partners Foundation.