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Randomized phase 2 window of opportunity trial comparing the effect of preoperative atirmociclib (PF-07220060) plus letrozole versus letrozole alone on Ki-67 tumor expression in postmenopausal women with HR+/HER2– breast cancer

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Objective

To evaluate the rate of complete cell cycle arrest (CCCA) following a 14-day, preoperative treatment with atirmociclib, a selective cyclin-dependent kinase 4 (CDK4) inhibitor, in combination with letrozole for patients with hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2–) early breast cancer (BC).

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Background

- In previous BC clinical trials, complete cell cycle arrest (CCCA; defined as Ki-67 ≤ 2.7%) in the surgical specimen after neoadjuvant treatment was correlated with relapse-free survival.[1,2]
- A cyclin-dependent kinase 4/6 (CDK4/6) inhibitor combined with endocrine therapy improves progression-free survival and/or overall survival for patients with HR+/HER2– metastatic BC.[3]
- Cytopenia is a major dose-limiting toxicity resulting from CDK4/6 inhibitor use; neutropenia is believed to be mediated mainly by inhibition of CDK6 rather than of CDK4.[4]
- Atirmociclib (PF-07220060) is a novel, highly potent and selective inhibitor of CDK4.
- In preclinical studies, atirmociclib induced G1 cell cycle arrest in BC cell lines and significantly inhibited the growth of HR+/HER2– tumor xenografts, which are known to have a high degree of CDK4 dependency.
- Preliminary results from a phase 1/2a multipart trial assessing atirmociclib in patients with HR+/HER2– metastatic BC whose cancer had progressed during prior treatment with a CDK4/6 inhibitor have demonstrated encouraging efficacy, safety, and tolerability.[5,6]
- Based on these findings, the aim of this study is to evaluate the potential impact of atirmociclib in combination with letrozole when used as preoperative treatment for patients with HR+/HER2– early BC.

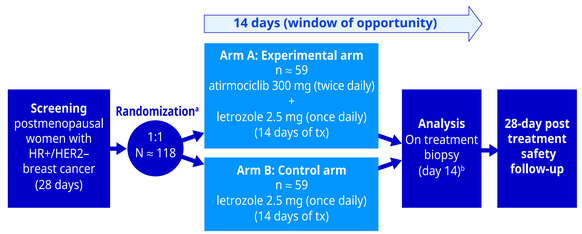
Materials and methods

- This window of opportunity study is an international (16 countries, > 80 proposed sites), phase 2, open-label, randomized controlled trial (FourLight-2; NCT06465368).

STUDY DESIGN

- The biological activity of atirmociclib plus letrozole versus letrozole alone on Ki-67 expression in tumors after 14 days of treatment will be assessed in the preoperative setting for postmenopausal women aged 18 years or older with newly diagnosed and treatment-naive HR+/HER2– BC (**Figure 1**).
- Patients will be randomized 1:1 to each treatment arm.
- Biopsies will be performed prior to treatment (baseline biopsy) and on day 14 of treatment (on-treatment biopsy).

Figure 1. FourLight-2 study design



KEY INCLUSION CRITERIA

- Postmenopausal women aged ≥ 18 years
- Newly diagnosed, treatment-naive, histologically confirmed HR+/HER2– BC (locally assessed)
- Ki-67 score of ≥ 10% (locally or centrally assessed) on primary biopsy
- Primary tumor size that is ≥ 1.5 cm
- ECOG performance status of 0 or 1

KEY EXCLUSION CRITERIA

- Any other active malignancy in the 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or cervical carcinoma in situ
- History of allergy or reaction to study drug components
- Inadequate bone marrow, renal, and/or liver function
- Prior and/or current systemic therapy (eg, chemotherapy or hormonal therapy), radiation, surgery, or any investigational agents for the treatment of BC
- Use of hormone replacement therapy (including progesterone therapy) or any other estrogen-containing medication (including vaginal estrogen) in the 2 weeks prior to the diagnostic tissue sample being taken

[a]Stratification factors: baseline Ki-67 score and tumor size.
[b]After day 14, patients will receive physician's choice of standard of care.
BC, breast cancer; ECOG, Eastern Cooperative Oncology Group; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; tx, treatment.

TREATMENT INTERVENTIONS

- Patients randomly assigned to the experimental arm (Arm A) will receive atirmociclib as three 100 mg tablets (ie, 300 mg in total), orally, twice daily, with food, continuously for 14 days plus letrozole as one 2.5 mg tablet, orally, once daily, continuously for 14 days.
- Patients randomly assigned to the control arm (Arm B) will receive letrozole as one 2.5 mg tablet, orally, once daily, continuously for 14 days.

STUDY ENDPOINTS

- Key study endpoints are summarized in **Table 1.**

Table 1. Key study endpoints

Endpoints	Assessments
Primary	• CCCA (Ki-67 ≤ 2.7%) rates at day 14 (centrally assessed)
Secondary	• Incidence of all AEs, serious AEs, and AEs leading to study drug discontinuation • ctDNA measurements at baseline and day 14 • C_{trough} and peri-biopsy plasma concentration of atirmociclib • Ki-67 staining (centrally assessed)
Exploratory	• Spatial omics of both tumor and stromal cells • Allelic variants of drug-metabolizing enzymes and transporters • Tumor gene alterations in ctDNA • Tumor gene expression profiles

AE, adverse event; CCCA, complete cell cycle arrest; ctDNA, circulating tumor DNA; C_{trough}, plasma trough concentration.

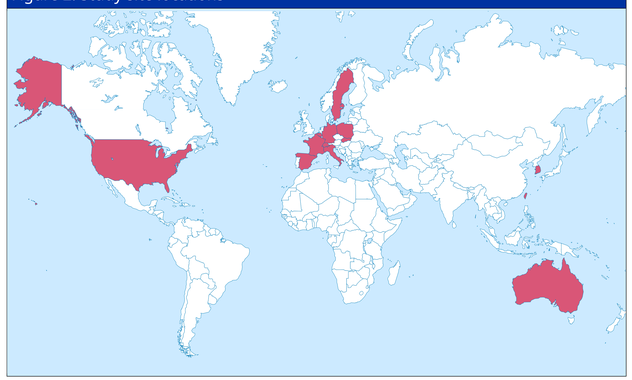
STATISTICAL CONSIDERATIONS

- Participants with evaluable Ki-67 results from baseline (locally or centrally assessed) and day 14 (centrally assessed) visits will be included in the primary analysis.
- No formal hypotheses will be tested in this study.
- The rate of patients with CCCA in each group will be calculated along with the two-sided 95% confidence interval. Bayesian analysis will be performed to assess the CCCA rates using posterior probabilities.
- The estimated total number of enrolled participants is 118 under the assumption that about 85% of the enrolled participants will have Ki-67 evaluable data or about 50 participants per arm.

TRIAL ENROLLMENT INFORMATION

- Trial registration: NCT06465368.
- Study start: July 2024.
- Number of enrolled patients (as of October 2024): 2 (of 118 planned).
- Study site locations: Australia, Belgium, France, Germany, Italy, Republic of Korea, Poland, Slovakia, Spain, Sweden, Switzerland, Taiwan, and the USA (**Figure 2).**

Figure 2. Study site locations



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