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Randomized phase 3 clinical trial evaluating atirmociclib plus letrozole versus a CDK4/6 inhibitor plus letrozole as first-line treatment for patients with HR+/HER2– advanced/metastatic breast cancer

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Objective

To evaluate whether atirmociclib plus letrozole can improve clinical outcomes relative to a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i; abemaciclib, palbociclib, or ribociclib) plus letrozole for patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) advanced/metastatic breast cancer (a/mBC) not previously treated with any systemic anticancer treatment in the advanced/metastatic setting.

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Background

- CDK4/6i, in combination with endocrine therapy (ET), have improved survival outcomes when used as first-line treatment[1] and are considered standards of care for patients with HR+/HER2– a/mBC.[2]
- Although CDK4/6i provide clinical benefit, some patients exhibit primary resistance,[3] while many others develop acquired resistance over time, ultimately limiting the sustained efficacy of CDK4/6i.[4]
- Toxicity and associated adverse events (AEs) have been observed with CDK4/6i, potentially leading to reduced time on treatment and poorer patient quality of life.[5]
- Consequently, there is an unmet medical need for the development of more efficacious and tolerable therapies for the treatment of HR+/HER2– a/mBC.
- Atirmociclib (PF-07220060) is an oral, potent CDK4i that drives cell cycle arrest and cellular senescence through the selective inhibition of CDK4;[6] atirmociclib may provide improved efficacy relative to CDK4/6i while minimizing hematopoietic effects that are thought to be due to inhibition of CDK6 inhibition.[6]
- An ongoing, first-in-human, phase 1/2a study has reported data supporting the efficacy, safety, and tolerability of first-line atirmociclib plus ET in patients with HR+/HER2– a/mBC (cohort 2B; n=34).[7]
- After a median follow-up period of 24.8 months (data cutoff: February 21, 2025), 69.7% of patients (23/33) with measurable disease at baseline achieved a confirmed objective response, while the clinical benefit rate was 93.9% (31/33).[7]
- The most common treatment-related, treatment-emergent AEs (TRAEs) were neutropenia (61.8%; 26.5% grade 3) and leukopenia (41.2%; no grade 3); only 1 patient discontinued atirmociclib due to a TRAE.[7]

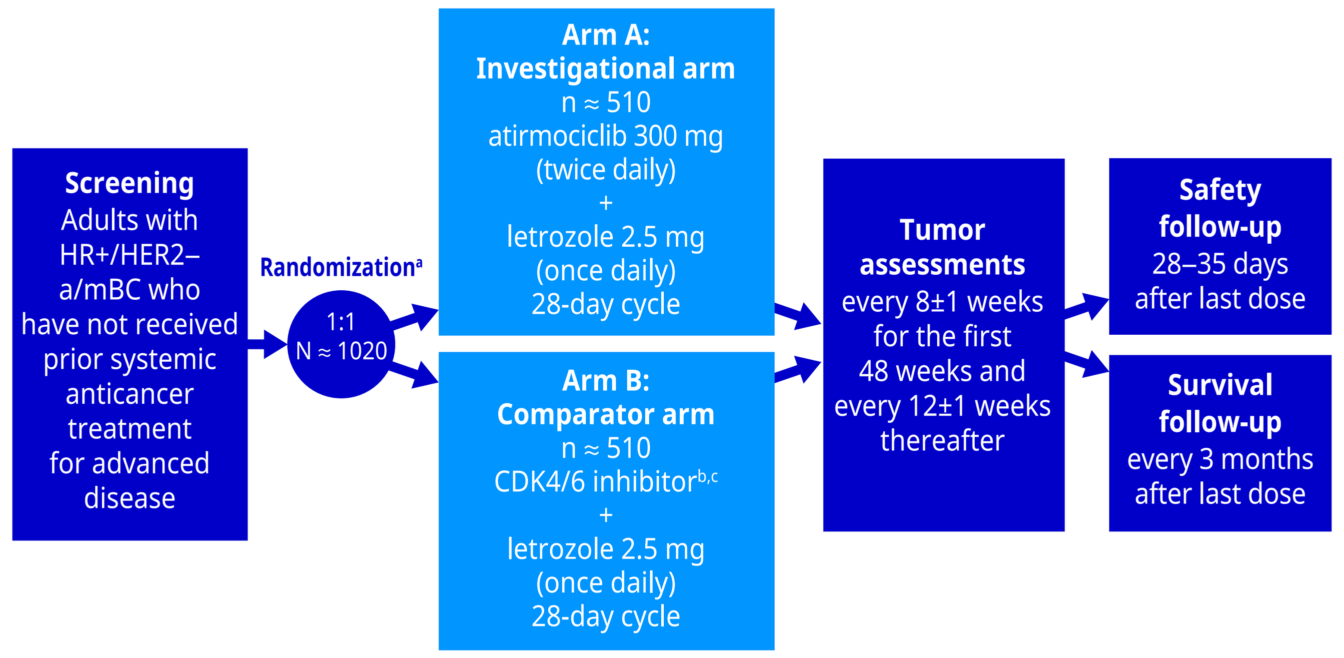
Materials and methods

- This is an international (27 countries, 225 sites), phase 3, open-label, randomized study (FourLight-3; NCT06760637) conducted in patients with HR+/HER2– a/mBC who have not received any prior systemic anticancer treatment for advanced/metastatic disease.

STUDY DESIGN

- Following screening, patients will be randomized 1:1 to either treatment arm (**Figure 1**).

Figure 1. FourLight-3 study design



KEY INCLUSION CRITERIA

- Adults aged ≥18 years (or minimum age of consent)
- Pre/perimenopausal patients must receive therapy with an LHRH agonist prior to the first dose of study intervention (if not already ongoing) and continue throughout the study
- Histologically confirmed HR+/HER2– breast cancer (locally assessed), with evidence of a/mBC, not amenable to surgical resection or radiation therapy with curative intent
- Previously untreated with any systemic anticancer therapy for a/mBC
- Either measurable disease or nonmeasurable bone-only disease per RECIST v1.1
- Resolution of acute effects of any prior therapy to no worse than CTCAE Grade 1
- ECOG performance status ≤2

KEY EXCLUSION CRITERIA

- Recurrence during or within 12 months after the last dose of prior (neo)adjuvant ET or CDK4/6i
- 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
- A history of CNS metastases

[a]Patients will be stratified by site of disease (visceral vs nonvisceral), *de novo* a/mBC (yes vs no), and investigator's intended choice of CDK4/6 inhibitor (abemaciclib vs palbociclib vs ribociclib).

[b]Investigator's choice: abemaciclib, palbociclib or ribociclib.

[c]Switching to another CDK4/6i after randomization is not permitted.

a/mBC, advanced/metastatic breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HR+/HER2–, hormone receptor-positive/human epidermal growth factor receptor 2-negative; LHRH, luteinizing hormone-releasing hormone; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

TREATMENT INTERVENTIONS

- Patients randomly assigned to the interventional arm (Arm A) will self-administer atirmociclib 300 mg, orally, twice daily, with food, continuously for 28 days (one cycle) plus letrozole 2.5 mg, orally, once daily, continuously for 28 days.
- Patients randomly assigned to the comparator arm (Arm B) will self-administer one of the following 3 CDK4/6i (abemaciclib/palbociclib/ribociclib) as per physician's choice (as per locally approved product label) plus letrozole 2.5 mg.

STUDY ENDPOINTS

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

Table 1. Key study endpoints

Endpoints	Assessments	
Primary	• PFS by BICR	
Key Secondary	• OS	
Secondary	Efficacy • PFS by investigator • Objective response (BICR and investigator) • Duration of response (BICR and investigator) • Clinical benefit response (BICR and investigator) Safety and tolerability • Adverse event type, incidence, severity, seriousness, and relationship to study medications	Health-related quality of life • Change from baseline in: – EORTC QLQ-C30 – EORTC QLQ-BR42 – BPI-SF – EQ-5D-5L • Time to deterioration in EORTC QLQ-C30, EORTC QLQ-BR42 and BPI-SF • Proportion of patients with deterioration, improvement, or no change in trouble by side effect per EORTC item library question 168 ctDNA assessment • ctDNA changes from baseline and association(s) with clinical outcome

BICR, blinded independent central review; BPI-SF, Brief Pain Inventory-Short Form; BR42, Breast Cancer Module; ctDNA, circulating tumor DNA; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, European Quality of Life 5 Domain 5 Level Scale; OS, overall survival; PFS, progression-free survival; QLQ, Quality of Life Questionnaire.

STATISTICAL CONSIDERATIONS

- The two treatment arms will be compared using a stratified log-rank test with a hazard ratio and the 95% confidence interval estimated using a stratified Cox model.
- The study is designed to have two interim analyses of PFS for futility and efficacy, respectively, and two interim analyses of overall survival (OS) for efficacy.
- Multiplicity will be controlled to maintain the overall type I error rate at a one-sided alpha of 0.025 for the analysis of PFS and OS.

TRIAL ENROLLMENT INFORMATION

- Trial registration: NCT06760637
- Study start date: January 2025
- Number of enrolled patients (as of September 2025): 507 (of 1020 planned)
- Study site locations: Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, China, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Republic of Korea, Mexico, Poland, Slovakia, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, United States (**Figure 2**).

Figure 2. Study site locations