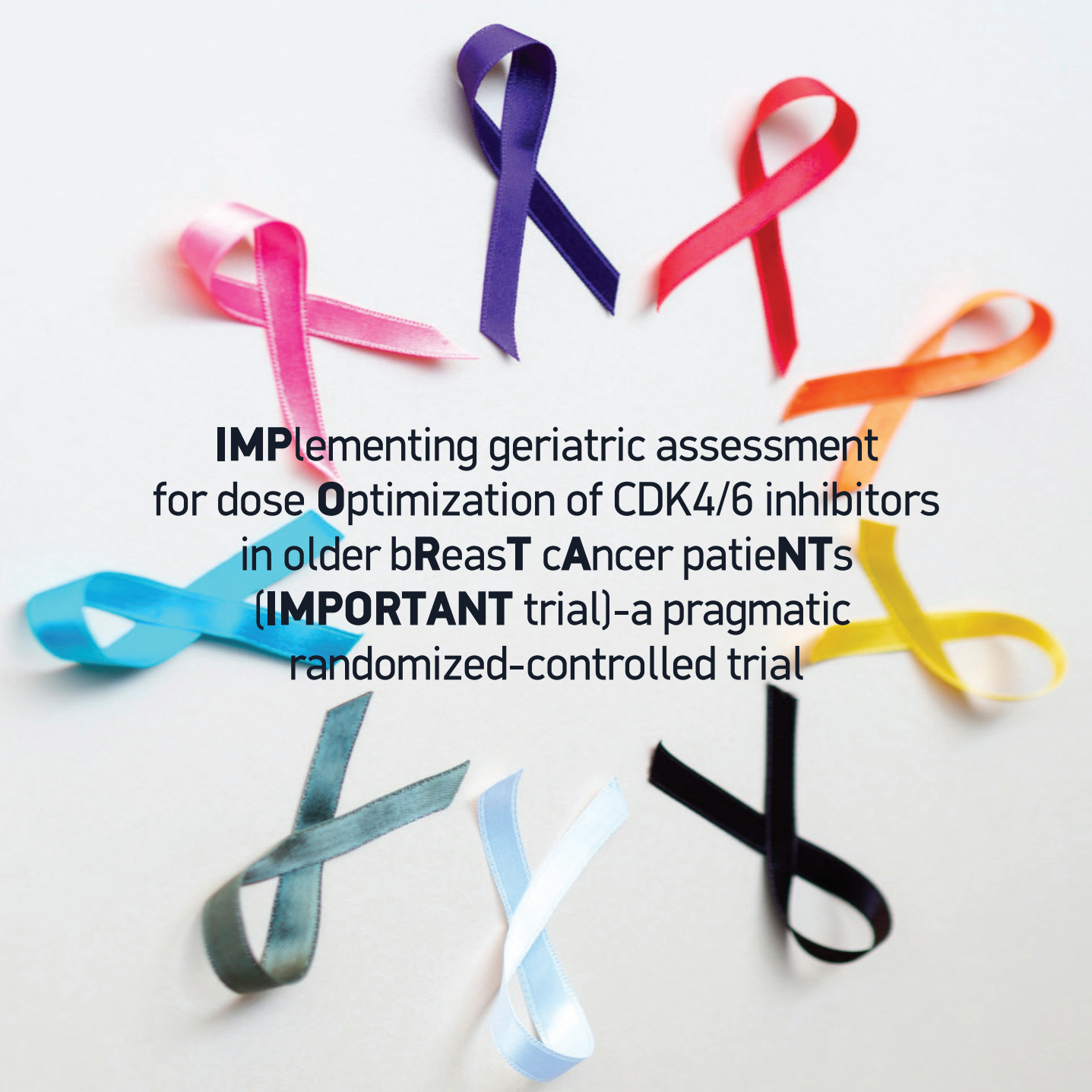


A healthcare professional, likely a nurse or doctor, is shown from the chest up, wearing light blue scrubs and a stethoscope. They are holding a large, light pink heart-shaped sign in front of their chest with both hands. The sign features the word "IMPORTANT" in a dark blue, serif font. The letter "O" is replaced by a colorful, pixelated icon of a virus or microorganism. The background is a soft, out-of-focus light blue.

IMP  RTANT



GRANT AGREEMENT No 101104589



**IM**plementing geriatric assessment  
for dose **O**ptimization of CDK4/6 inhibitors  
in older **bReasT cANcer** patient**S**  
(**IMPORTANT** trial)-a pragmatic  
randomized-controlled trial

# Project Aim

The IMPORTANT project is dedicated to designing and conducting a pragmatic clinical study to optimize the dose of cyclin-dependent kinases (CDK) 4/6 inhibitors among older patients with advanced breast cancer. This innovative research will provide high-level evidence (level I) and aims to change current clinical practice.

## Rationale

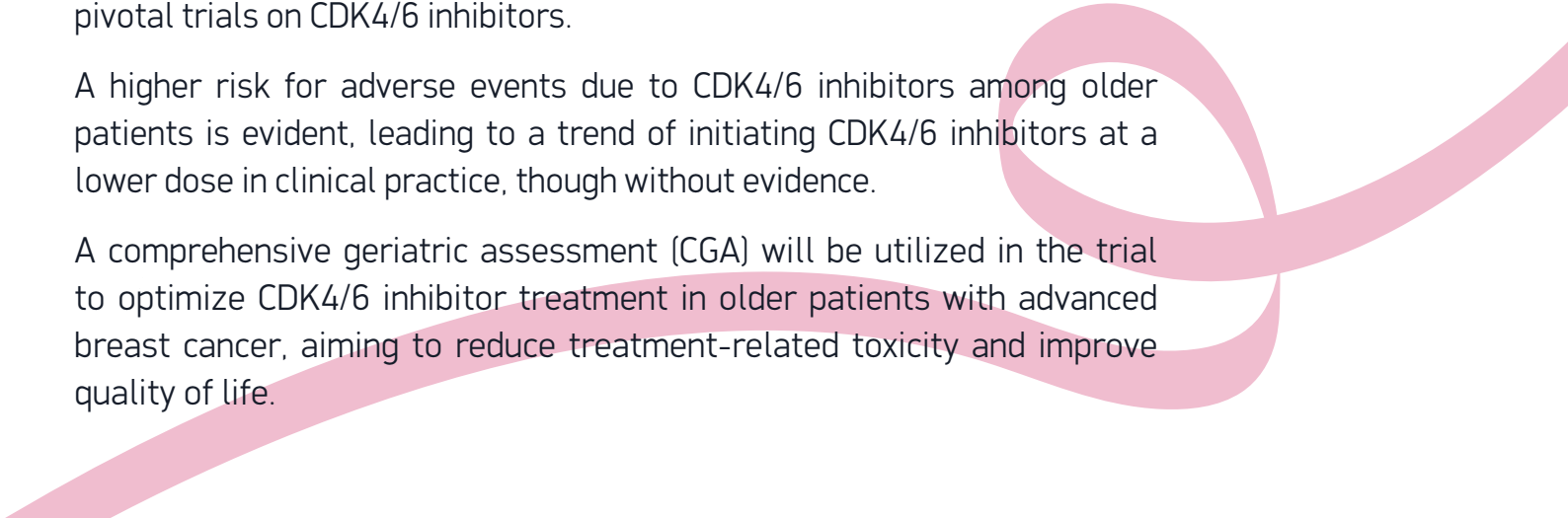
The combination of endocrine therapy with CDK4/6 inhibitors is the standard of care as an initial treatment approach in patients with advanced hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

CDK4/6 inhibitors are a class of medicines that interrupt the process through which breast cancer cells divide and multiply by targeting specific proteins known as the cyclin-dependent kinases 4 and 6.

Older cancer patients are underrepresented in clinical trials, including pivotal trials on CDK4/6 inhibitors.

A higher risk for adverse events due to CDK4/6 inhibitors among older patients is evident, leading to a trend of initiating CDK4/6 inhibitors at a lower dose in clinical practice, though without evidence.

A comprehensive geriatric assessment (CGA) will be utilized in the trial to optimize CDK4/6 inhibitor treatment in older patients with advanced breast cancer, aiming to reduce treatment-related toxicity and improve quality of life.





# **INFORMATION ON THE PROJECT**

**Study Type:** A multi-national, open-label, pragmatic randomized controlled trial with non-inferiority approach.

**Focus:** Comparison of lower initial dose versus full dose of CDK4/6 inhibitors combined with endocrine therapy in older, vulnerable/frail patients with advanced HR-positive/HER2-negative breast cancer.

**Comprehensive Geriatric Assessment (CGA):** CGA will be performed on all eligible patients at baseline. Based on the CGA, two patient cohorts will be defined: fit older patients; and vulnerable/frail older patient.

**Clinical trial participants:** 495 male and female patients aged 70 years and older with advanced breast cancer from Finland, Greece, Italy, Norway, Spain, and Sweden. A total of 149 fit patients will be treated and followed, while 346 vulnerable/frail patients will be randomized.

**Participation Duration:** Participation will last up to five years.

**Project duration:** 60 months.

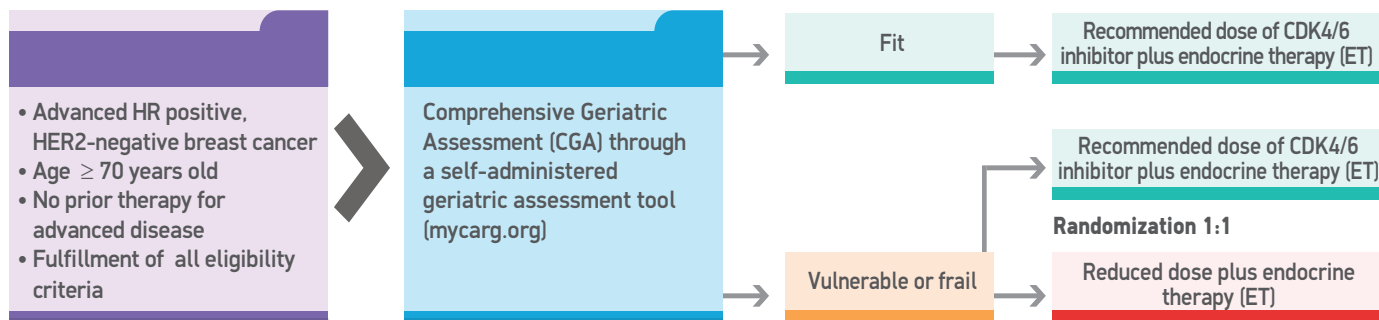
**Clinical Trial Inclusion Period:** 30 months starting in April 2024.

**Project consortium:** 19 partners from 11 countries, including hospitals, SMEs, universities, and patient advocacy organizations.

## PRAGMATIC APPROACH:

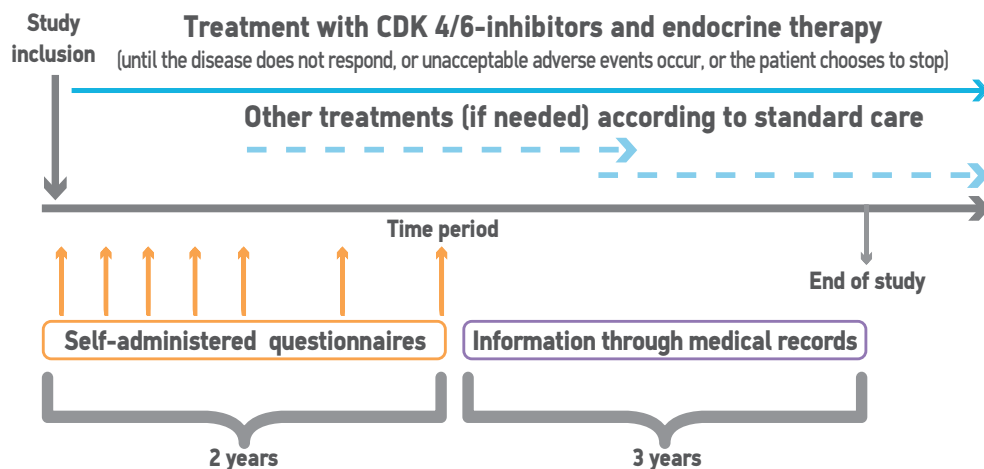
- Broad inclusion criteria;
- The follow-up strategy mirrors the current follow-up practices in clinical settings, without the need for additional blood tests or radiological examinations;
- The trial allows for a hybrid decentralized approach to reduce the burden of participation for older patients where the initial patient visit should be in-person, while subsequent visits for efficacy and toxicity evaluation can be conducted digitally according to local practices.

**Figure 1. IMPORTANT Trial Overview**



**Stratification factors at randomization:** a) type of CDK4/6 inhibitor (palbociclib vs. abemaciclib vs. ribociclib); b) type of endocrine therapy (i.e., ET; aromatase inhibitors vs. fulvestrant.); c) level of vulnerability (vulnerable vs. frail).

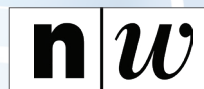
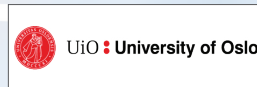
**Figure 2. Eligible patients' journey in the IMPORTANT trial**





**Table 1. Eligibility criteria for IMPORTANT trial**

Inclusion Criteria	Exclusion criteria
<p>Patients, either male or female, must be aged at least 70 years at the time of informed consent and diagnosed with advanced (locoregionally recurrent or metastatic) breast cancer that is not amenable to curative treatment;</p>	<p>Patients deemed unsuitable for treatment with CDK4/6 inhibitors by the treating physician;</p>
<p>Histologically or cytologically confirmed diagnosis of HR-positive (defined as estrogen-receptor <math>\geq</math> 1%), HER2-negative breast cancer, according on the analysis of the most recent tumor specimen by a local laboratory;</p>	<p>Patients with cognitive impairment (as assessed by the treating physician) that prevents the ability to complete the self-reported Comprehensive Geriatric Assessment (CGA).</p>
<p>No prior systemic treatment for advanced disease (recurrence during neo-/adjuvant endocrine therapy is allowed). A prior period of treatment with aromatase inhibitors or fulvestrant for up to 56 days before the CDK4/6 inhibitor initiation is allowed, provided there is no disease progression during this time-frame;</p>	<p>Contraindications as outlined in the summary of product characteristics for the CDK4/6 inhibitors;</p>
<p>Adjuvant treatment with CDK4/6 inhibitors is allowed provided a disease-free interval of more than 12 months from the end of treatment;</p>	<p>Presence of visceral crisis, lymphangitis carcinomatosa, or leptomeningeal carcinomatosa;</p>
<p>Adequate organ function as defined in the summary of product characteristics for the CDK4/6 inhibitors;</p>	<p>History of any other cancer (except for non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years;</p>
<p>Able to understand and give consent in English or in the native language of each participating country.</p>	<p>Participation in another interventional trial.</p>



# IMP RTANT



IMPORTANT-PROJECT.COM

**Join us in transforming the treatment landscape for older breast cancer patients!**



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