PALbociclib CoLlaborative Adjuvant Study:
A randomized phase III trial of Palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for hormone receptor positive (HR+) / human epidermal growth factor receptor 2 (HER2)-negative early breast cancer

Published: 08-07-2016
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This study has been transitioned to CTIS with ID 2024-514841-12-00 check the CTIS register for the current data. Primary Objective:To compare invasive disease-free survival (iDFS) for the combination of at least 5 years endocrine therapy and 2-year...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON47438

Source
ToetsingOnline

Brief title
PALLAS

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
HR+/HER2 negative early breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Alliance Foundation Trials (AFT) and Austrian Breast and Colorectal Cancer Study Group (ABCSG)
Source(s) of monetary or material Support: Industry

Intervention

Keyword: HR+/HER2 negative early breast cancer, Palbociclib, Phase 3

Outcome measures

Primary outcome

Primary Endpoint:

Invasive disease-free survival (iDFS) defined according to STEEP criteria.

Secondary outcome

Secondary Endpoints:

(1) Invasive disease-free survival (iDFS) excluding second primary invasive

cancers of non-breast origin as an event.

(2) Overall Survival (OS).

(3) Locoregional recurrences-free survival (LRRFS) defined as the composite of

local/regional ipsilateral recurrence, contralateral invasive breast cancer or

death from any cause.

(4) Distant recurrence free survival (DRFS) is defined according to STEEP

criteria as the composite of distant recurrence or death from any cause.

(5) Adverse Events.

Clinical Science Endpoints:

(1) Adherence measured by Drug Diary, Morisky Medication Adherence Scale,

Medication Adherence and McHorney Brief Estimator questionnaires.

(2) Primary endpoint (iDFS) effected by baseline body mass index (BMI).

Study description

Background summary

Although many patients with HR+/HER2- breast cancer may be cured of their disease with optimal local and systemic therapy, a significant number of patients with stage II and III disease will experience disease recurrence. Adjuvant endocrine therapy for breast cancer can be extremely effective, particularly with extension beyond 5 years, however disease recurrence can occur, with risk distributed over the decades following initial diagnosis. Methods to improve the efficacy of endocrine therapy, and delay the onset of resistance, are needed.

HR+ breast cancer biologically may demonstrate features suggestive of sensitivity to CDK4/6 inhibition with agents such as palbociclib. Given the demonstrated activity and safety of palbociclib in the first-line treatment of metastatic HR+/ HER2- breast cancer, supporting FDA approval, there is interest in whether the benefits of CDK4/6 inhibition may translate into the adjuvant setting. The purpose of the PALLAS study is to determine whether the addition of palbociclib to adjuvant endocrine therapy will improve outcomes over endocrine therapy alone for HR+/HER2- early breast cancer. Assessment of a variety of correlative analysis, including evaluation of the effect of palbociclib in genomically defined tumor subgroups, is planned.

Study objective

This study has been transitioned to CTIS with ID 2024-514841-12-00 check the CTIS register for the current data.

Primary Objective:
To compare invasive disease-free survival (iDFS) for the combination of at least 5 years endocrine therapy and 2-year palbociclib treatment versus at

least 5 years endocrine therapy alone in patients with histologically confirmed HR+/HER2- invasive early breast cancer (EBC).

Secondary Objectives
To compare the following endpoints:
- iDFS excluding second primary invasive cancers of non-breast origin
- distant recurrence-free survival (DRFS)
- locoregional recurrences-free survival (LRRFS)
- overall survival (OS).
To compare the safety of 2 years of palbociclib with adjuvant endocrine therapy versus adjuvant endocrine therapy alone.

Translational Science Principal Objective
To compare baseline tumor tissue to determine whether there is prognostic or predictive utility for defined genomic subtypes (luminal A, luminal B and non-luminal) with respect to iDFS and OS.

Study design

This is a prospective, two arm, international, multicenter, randomized, open-label Phase III study evaluating the addition of 2 years of palbociclib to standard adjuvant endocrine therapy for patients with HR+ / HER2- early breast cancer (EBC).

Endocrine adjuvant therapy may have started before randomization and be ongoing at the time of randomization.

Eligible patients will be receiving standard adjuvant endocrine therapy for HR+/ HER 2- early breast cancer.

A total of 4600 patients will be randomized in a 1:1 ratio to:
Arm A: palbociclib at a dose of 125 mg orally once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for a total duration of 2 years, in addition to standard adjuvant endocrine therapy for a duration of at least 5 years.
Arm B: standard adjuvant endocrine therapy for a duration of at least 5 years.

Standard endocrine therapy (also referred to as background treatment) can be tamoxifen or aromatase inhibitor with or without LHRH agonist.

Patients will be randomized within strata defined by:
- natomic stage (IIA vs IIB/III) assessed by pathologic staging, or by clinical staging if pre-operative therapy was given with the higher stage determining eligibility
- Neo/adjuvant chemotherapy (yes vs no)
- Age (<= 50 vs > 50 years)
- Geographic region (North America vs Europe vs Other).

Patients randomized into Arm A will receive protocol-assigned palbociclib therapy for the planned duration of 2 years or until diagnosis of invasive local, regional or distant recurrence, diagnosis of secondary invasive malignancy (except ductal carcinoma of the breast, cervical cancer in situ, and non- metastatic non-melanomatous skin cancers), unacceptable toxicity, patient withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Intervention

Eligible patients will be receiving standard adjuvant endocrine therapy for HR+/ HER 2- early breast cancer.
A total of 4600 patients will be randomized in a 1:1 ratio to:
Arm A: palbociclib at a dose of 125 mg orally once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for a total duration of 2 years, in addition to standard adjuvant endocrine therapy for a duration of at least 5 years.
Arm B: standard adjuvant endocrine therapy for a duration of at least 5 years.

Study burden and risks

HR+ breast cancer is the most commonly diagnosed subset of breast cancer, and affects thousands of patients every year.
Despite the efficacy of up to 10 years of adjuvant endocrine therapy, a percentage of patients will relapse with incurable metastatic disease, with risk extending for many years after initial diagnosis.
Therefore, improving the efficacy of adjuvant endocrine therapy would be of extraordinary benefit to a large number of breast cancer patients, and is an unmet medical need.

Data from PALOMA-1 has demonstrated a significant prolongation of median progression-free survival with the combination of palbociclib and letrozole compared with letrozole alone.
The toxicity profile of palbociclib at the dose and schedule similar to the one that will be used in the PALLAS study was moderate, with neutropenia being the most frequent treatment related adverse event.
The clinical picture of neutropenia seen with the palbociclib/letrozole combination in PALOMA-1 is notable for being quickly reversible, noncumulative and uncomplicated and managed without the use of growth stimulating factors.
The data generated from PALOMA-1 has supported accelerated approval by FDA in the US of palbociclib in combination with letrozole for advanced HR+/HER2- breast cancer.

In the PALLAS trial, all study participants are expected to have undergone adequate initial local treatment for their breast cancer including surgical resection, with or without adjuvant radiotherapy.

Participants are also expected to have selected an appropriate systemic therapy plan, with or without chemotherapy and have decided to receive endocrine therapy.

All patients, regardless of randomization arm, will receive standard adjuvant endocrine treatment according to institutional standards.
It is not expected that toxicity of palbociclib will reduce compliance with endocrine treatment.

There are no obvious differences in the clinical and laboratory safety profile between patients taking palbociclib for less than 12 months compared to those taking the drug for 12 months or longer based on data collected in clinical studies to date.
It is concluded that the data available do not identify any safety concerns associated with long term administration of palbociclib.
Given the increasing use of longer duration endocrine therapy and the known prolongation of cancer recurrence risk well beyond 5 years, palbociclib therefore will be administered for 2 years.
In addition, participating patients in the current trial will have marginal additional burden due to investigations required for study participation (e.g. additional visits at the site, additional blood tests, and completion of questionnaires).
However, the option to receive a treatment potentially significantly improving iDFS in this population is considered to balance uncertainties of the toxicity profile of palbociclib and the additional burden related to study investigations.

Contacts

Public
Alliance Foundation Trials (AFT) and Austrian Breast and Colorectal Cancer Study Group (ABCSG)

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Vienna 1190
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Scientific
Alliance Foundation Trials (AFT) and Austrian Breast and Colorectal Cancer Study Group (ABCSG)

Nussdorfer Platz 8
Vienna 1190
AT

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

(1) Signed informed consent obtained prior to any study specific assessments and procedures.
(2) Age >=18 years (or per national guidelines).
(3) Premenopausal and postmenopausal women or men with Stage II (Stage IIA limited to a max. of 1000 patients) or Stage III early invasive breast cancer per AJCC Breast Cancer Staging version 7 /UICC . Baseline staging to document absence of metastatic disease is not required, however is recommended as determined by institutional practice.
(4) Patients with multicentric and/or multifocal and/or bilateral early invasive breast cancer whose histopathologically examined tumors all meet pathologic criteria for ER+ and/or PR+ and HER2-.
(5) Patients must have histologically confirmed hormone receptor positive (ER+ and/or PR+), HER2-, early invasive breast cancer. ER, PR and HER2 measurements should be performed acc. to institutional guidelines, in a CLIA-approved setting in the US or certified laboratories for Non-US regions. Cut-off values for positive/negative staining should be in accordance with current ASCO/CAP guidelines. Patients with equivocal HER2 in situ hybridization results according to current ASCO/CAP guidelines are eligible, as long as they have not received and are not scheduled to receive anti-HER2 treatment. Testing may occur on diagnostic core or surgical tumor tissue.
(6) Patients must have undergone adequate (definitive) breast surgery for the current malignancy.
(7) A formalin-fixed paraffin-embedded (FFPE) tumor tissue block must be transmitted to a central sample repository and confirmation of receipt must be available prior to randomization.
(8) ECOG performance status 0-1.
(9) Patients must be able and willing to swallow and retain oral medication without a condition that would interfere with enteric absorption.
(10) Serum or urine pregnancy test must be negative within 7 days of randomization in women of childbearing potential. Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before randomization, as determined by local practice, or who have undergone bilateral

oophorectomy, total hysterectomy, or bilateral tubal ligation. Women of childbearing potential and male patients randomized into treatment Arm A or B must use adequate contraception for the duration of protocol treatment and for 6 months after the last treatment with palbociclib if they are in arm A. In addition, patients receiving standard adjuvant endocrine therapy (Arm A and Arm B) should use adequate contraception in accordance with the specific medication requirements (e.g. SmPC).Prior Treatment Specifics
(11) Patients may or may not have received neo/adjuvant therapy, but must be after last dose of chemotherapy and/or biologic therapy and must have sufficient resolution of side effects per physician assessment at the time of randomization.
(12) Patients may or may not have received breast/axilla/post-mastectomy chest wall radiotherapy, but must be after last dose of radiotherapy and must have sufficient resolution of side effects per physician assessment at the time of randomization.
(13) Patients must have sufficient resolution of any surgical side effects from the last surgery per physician assessment with no active wound healing complications at the time of randomization.
(14) Patients must either be initiating or have already started adjuvant hormonal treatment. Patients may already have initiated endocrine therapy at the time of randomization, but randomization must take place within 12 months of date of histological diagnosis and within 6 months of initiating standard adjuvant endocrine therapy. Patients who received neoadjuvant endocrine therapy are eligible as long as they are randomized within 12 months of initial histological diagnosis and after completing no more than 6 months of adjuvant endocrine therapy. Patients may be receiving either tamoxifen or aromatase inhibitor (AI: letrozole, anastrozole, or exemestane). For premenopausal patients and men, concurrent LHRH agonist use is allowable and may also be ongoing at the time of randomization. If a LHRH agonist was used for ovarian protection during neo / adjuvant chemotherapy it is allowable and shall not be taken into account for calculations regarding the 6 months standard adjuvant endocrine therapy.Baseline Body Function Specifics
(15) Absolute neutrophil count >= 1,500/mm3
(16) Platelets >= 100,000/ mm3
(17) Hemoglobin >= 10g/dL
(18) Total serum bilirubin <= ULN; or total bilirubin <= 3.0 × ULN with direct bilirubin within normal range in patients with documented Gilbert*s Syndrome.
(19) Aspartate amino transferase (AST or SGOT) and alanine amino transferase (ALT or SGPT) <= 1.5 × institutional ULN.
(20) Serum creatinine below the upper limit of the institutional normal range (ULN) or creatinine clearance (or glomerular filtration rate (GFR) >= 60 mL/min/1.73 m2 for patients with serum creatinine levels above institutional ULN.

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Exclusion criteria

(1) Concurrent therapy with other Investigational Products.
(2) Prior therapy with any CDK inhibitor.
(3) Patients with Stage I or IV breast cancer are not eligible. Baseline staging to document absence of metastatic disease is not required, however is recommended as determined by institutional practice.
(4) History of allergic reactions attributed to compounds of chemical or biologic composition similar to palbociclib.
(5) Patients receiving any medications or substances that are potent inhibitors or inducers of CYP3A isoenzymes within 7 days of randomization.
(6) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, diabetes, or psychiatric illness/social situations that would limit compliance with study requirements. Ability to comply with study requirements is to be assessed by each investigator at the time of screening for study participation.
(7) Pregnant women, or women of childbearing potential without a negative pregnancy test (serum or urine) within 7 days prior to randomization, irrespective of the method of contraception used, are excluded from this study because the effect of palbociclib on a developing fetus is unknown. Breastfeeding must be discontinued prior to study entry.
(8) Patients with a history of any malignancy are ineligible except for the following circumstances:
• Patients with a malignancy history other than invasive breast cancer are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy.
• Patients with the following cancers are eligible, even if diagnosed and treated within the past 5 years: ductal carcinoma in situ of the breast, cervical cancer in situ, and non-metastatic non-melanomatous skin cancer.
(9) Patients are not eligible if they have previously received endocrine therapy within 5 years prior to diagnosis of the current malignancy. This includes use for prophylactic reasons, including treatment of osteoporosis or cancer prevention with tamoxifen, raloxifene or AI. Patients may concurrently receive bisphosphonates or rank ligand inhibitors while on this study if necessary for treatment or prevention of osteopenia or osteoporosis.
(10) Patients on combination antiretroviral therapy, i.e. those who are HIV-positive, are ineligible because of the potential for pharmacokinetic interactions or increased immunosuppression with palbociclib.
(11) Patients with clinically significant history of chronic liver disease, including chronic / active viral or other known hepatitis, current alcohol abuse, or cirrhosis, etc.
(12) Patients receiving concurrent exogenous hormone therapy (hormone

replacement therapy, oral or any other hormonal contraceptives such as hormonal contraceptive coil, etc.) are not eligible but topical vaginal estrogen therapy is allowable.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-05-2017
Enrollment:	30
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Ibrance
Generic name:	Palbociclib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	08-07-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	14-12-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-07-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-09-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-10-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-10-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-01-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-06-2018
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-06-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-12-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-10-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-11-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	30-07-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-08-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-06-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-06-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-11-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	01-02-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-514841-12-00
EudraCT	EUCTR2014-005181-30-NL
ClinicalTrials.gov	NCT02513394/IND126003
CCMO	NL57161.100.16