The use of single cell genomics to identify chromosomal alterations driving resistance to palbociclib in metastatic breast cancer patients

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

Summary

ID

NL-OMON52225

Source
ToetsingOnline

Brief title
PALETTE

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Metastatic breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Pfizer

Intervention

Keyword: circulating tumor cells, metastatic breast cancer, palbociclib, resistance mechanisms

Outcome measures

Primary outcome

Newly identified and/or enriched chromosomal alterations at PD compared to

baseline within 8 patients treated with palbociclib and initial disease

control.

Secondary outcome

- The percentage of the isolated single CTCs in which the obtained WGA product

pass our quality criteria.

- The percentage of the successfully whole genome amplified CTCs in which we

obtain a chromosomal profile passing our quality criteria with respect to

library concentration, read depth, and signal-to-noise ratio (estimated by the

median absolute deviation value (MAD) of the profile)

- The levels of ctDNA in patients obtained in peripheral blood before and after

treatment with palbociclib

Study description

Background summary

Addition of the CDK4/6 inhibitor palbociclib to endocrine treatment greatly increases the median progression-free survival (PFS) of patients with

ER-positive, HER2-negative metastatic breast cancer (MBC). However, ultimately all patients develop resistance to palbociclib and substantially more grade 3-4 toxicity is experienced by patients treated with palbociclib combination therapy compared to endocrine monotherapy. A better understanding of the molecular mechanisms that drive resistance to palbociclib in MBC patients is necessary to find the relevant biomarkers that can guide the just and timely administration of palbociclib and thereby reduce unnecessary toxicity. In vitro studies have already shown that resistance to CDK4/6 inhibitors appears associated with specific chromosomal copy number alterations (CNAs), but in patients no predictive biomarkers have been found to date.

Study objective

The primary objective of this study is to identify specific chromosomal alterations in circulating tumor cells (CTCs) in patients with metastatic breast cancer progressive on treatment with palbociclib. Secondary objectives are determining hte success rate of whole genome amplification of isolated single CTCs, the shallow sequencing of the WGA product and determining the level of ctDNA in MBC patients progressive on endocrine treatment.

Study design

Prospective, exploratory, single center study.

Study burden and risks

All patients are asked to undergo two leukapheresis procedures which will take a maximum of 2 hours per procedure. A maximum volume of calculated total body volume, which is approximately 5 L peripheral blood will be processed with the use of an Optia Spectra Cell Separator. Patients do not benefit from this study. The most common adverse events to be expected are pain or bruising at the venipuncture site (1-5%), apprehension or fainting associated with venipuncture (1-5%), fluid imbalance (0.01-0.1%) and citrate anticoagulant infusion-related symptoms resulting in tingling or buzzing around the mouth or fingers (20-50%). All patients will receive intravenous calcium to prevent this. The risk of adverse events associated with leukapheresis is considered negligible.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Adult women (>= 18 years of age) with proven diagnosis of adenocarcinoma of the breast with locoregional recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent.
2. Documentation of histologically or cytologically confirmed diagnosis of estrogen receptor (ER) expression >10% and/or progesterone receptor (PR) expression >10% breast cancer based on local laboratory results. Tumor must be HER2-negative as defined by ASCO-CAP guidelines (ref).
3. Patients starting the combination endocrine therapy + palbociclib as first or a subsequent treatment line for metastatic disease.
4. Patients must have evaluable disease as per RECIST v.1.1.
5. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study before any study-specific activity is performed.

Exclusion criteria

1. Pre-existing lymphedema in one or both arms, diagnosed by the treating medical oncologist

2. Patients with known hypersensitivity to the anticoagulant used for apheresis
3. Patients with inadequate cardiac function or severe cardiovascular comorbidity:
- Heart failure NYHA class III/IV
4. Hemoglobin level < 6.0 mmol/L
5. Coagulation disorders as defined by one of the following
- Coagulation disorder in medical history
- Platelet count < 40 x 109/L;
Patients without anticoagulant therapy which affects PT or APTT, when:
- PT > 1.5 x ULN or PT-INR > 1.5 x ULN
- APTT > 1.5 x ULN
Patients with anticoagulant therapy which affects PT or APTT, when:
- PT or APTT > 1.5 x the upper limit of the desired therapeutic window
- Total bilirubin >2.5 x ULN
6. Known chronic viral infections
7. Patients with a history of any other cancer, unless in complete remission requiring no active treatment, are excluded

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-02-2022
Enrollment:	48
Type:	Actual

Ethics review

Approved WMO

Date:	04-10-2021

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
CCMO	NL76953.078.21