Effect of the moderate CYP3A4-inhibitor erythromycin on the pharmacokinetics of palbociclib

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

Summary

ID

NL-OMON45801

Source
ToetsingOnline

Brief title
M18CYP - Palbociclib + moderate CYP3A4 inhibitor

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, mammary carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: NKI-AVL

Intervention

Keyword: CYP3A4, Drug-drug interaction, Palbociclib, Pharmacokinetics

Outcome measures

Primary outcome

The primary objective of this trial is to study the effect of the moderate CYP3A4 inhibitor erythromycin on the pharmacokinetics of palbociclib, measured as AUC0-24h, Cmax and Cmin.

Secondary outcome

The secondary objective of this trial is to compare the incidence and severity of adverse events with (a week) and without co-administration of the moderate CYP3A4 inhibitor erythromycin, according to CTC-AE v5.0.

Study description

Background summary

Palbociclib is an inhibitor of cyclin-dependent kinase 4 (CDK4) and CDK6, indicated for the treatment of hormone receptor positive, Her2 negative, locally advanced or metastatic breast cancer. Palbociclib exposure has been linked to toxicity, with a higher area under the concentration-time curve (AUC) being associated with a greater reduction in absolute neutrophil count. Common adverse reactions reported in patients receiving palbociclib are also fatigue, nausea, stomatitis and diarrhoea (>=20%), which can seriously hamper quality of life.

Palbociclib is metabolized by CYP3A4 and its exposure was significantly increased when co-administered with itraconazole (a strong CYP3A4 inhibitor), resulting in an increase in AUC0-inf and Cmax of 87% and 34%, respectively. Therefore, it is advised to avoid concomitant use of strong CYP3A4 inhibitors. If co-administration with a strong CYP3A4 inhibitor cannot be avoided, the daily palbociclib dose should be reduced to 75 mg (60% of standard dose). Although it is recommended by the FDA to evaluate the impact of moderate inhibitors in the case of clinically significant interactions with strong inhibitors, no management guidelines for concomitant use of palbociclib with

moderate CYP3A4 inhibitors have been reported.[2]

Yu et al published an physiologically based pharmacokinetic (PBPK) model, in which they simulated the effect of the moderate CYP3A4 inhibitors verapamil and diltiazem. They reported an increase in AUC and Cmax of 38% and 22% for verapamil; and 42% and 23% for diltiazem, respectively. The authors conclude that the risk of drug-drug interactions for palbociclib co-administered with moderate CYP3A4 inhibitors is relatively modest and that no dose adjustment is needed. However, a 40% increase in exposure could be clinically relevant, since higher palbociclib exposure is associated with increased toxicity like fatigue, nausea, stomatitis and diarrhoea which can seriously hamper quality of life (not only lab abnormalities).

Based on the above, we propose to conduct a randomized pharmacokinetic cross-over trial to study the effect of the moderate CYP3A4 inhibitor erythromycin on the pharmacokinetics of palbociclib. This study will provide enough data to guide future physicians and patients on dosing instructions and adverse events expectations when in daily care palbociclib is given to patients using a moderate CYP3A4 inhibitor.

Study objective

The primary objective of this trial is to study the effect of the moderate CYP3A4 inhibitor erythromycin on the pharmacokinetics of palbociclib, measured as AUC0-24h, Cmax and Cmin.
The secondary objective of this trial is to compare the incidence and severity of adverse events with (a week) and without co-administration of the moderate CYP3A4 inhibitor erythromycin, according to CTC-AE v5.0.

Study design

Randomized pharmacokinetic cross-over trial of palbociclib with and without erythromycin

Intervention

Palbociclib will be administered concomitant with erythromycin during 7 days of the study.

Study burden and risks

Patients will receive the standard dose of palbociclib (125 mg QD, 3-weeks on 1-week off) at all times during the study. Theoretically, the concomitant administration of palbociclib with erythromycin could lead to higher palbociclib exposure and thus give an increased risk of toxicities. However, the duration of this intervention is short (7 days).

Although erythromycin rarely gives toxicities, this is a minor risk for patients.

Since erythromycin could prolong the QTc interval, an ECG will be performed at screening. Patients with a prolonged QTc interval will be excluded.

In total, 28 PK samples of 3 mL will be drawn (14 samples at both Day 7 and Day 21).

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

• Histological or cytological proof of cancer for which palbociclib is considered standard care;
• Age >= 18 years;

• WHO performance status of 0, 1 or 2;
• Adequate organ function per judgement of the treating physician;
• Able and willing to undergo blood sampling for PK analysis.

Exclusion criteria

• Concomitant use of medication(s) which could influence the pharmacokinetics of palbociclib within 14 days or five half-lives of the drug (whichever is shorter) before start of the study, consisting of (but not limited to) CYP3A4-inhibitors/inductors
• Women who are pregnant or breast feeding;
• Patients with known alcoholism, drug addiction and/or psychiatric of physiological condition which in the opinion of the investigator would impair study compliance;
• Palbociclib related side effects that would require a dose reduction per judgement of the treating physician;
• QT duration corrected for heart rate > 450 ms or > 480 ms for subjects with bundle branch block.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-04-2019
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Erythrocine-ES
Generic name:	Erythromycin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Ibrance
Generic name:	Palbociclib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-11-2018
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-01-2019
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-03-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-12-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	30-12-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 20410
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2018-004032-29-NL
CCMO	NL67583.031.18
Other	nummer volgt nog
OMON	NL-OMON20410