The OPTIMAL study: Optimizing Performance of afiniTor by splitting Intake Moments and decreasing Adverse events whilst maintaining outcome quaLity.

Published: 20-11-2014
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To describe and compare pharmacokinetics of everolimus in a 10 mg QD and everolimus 5mg BID schedule, evaluated PK parameters will be a.o. Cmax/Cmin ratio, AUC, Cmax, Cmin, Tmax.

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

Summary

ID

NL-OMON41877

Source
ToetsingOnline

Brief title
N14OPT: The OPTIMAL study, 10 mg QD vs 5 mg BID Everolimus.

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast Cancer, HER-2 negative, Hormone Positieve

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Novartis,Novartis Pharma B.V.

Intervention

Keyword: Breast cancer, Everolimus, Pharmacokinetics

Outcome measures

Primary outcome

Pharmacokinetics of 10 mg QD vs 5 mg BID Everolimus: evaluated PK parameters

will be a.o. Cmax/Cmin ratio, AUC, Cmax, Cmin, Tmax.

Secondary outcome

Incidence and severity of stomatitis and other adverse events between the two

dosing schedules, according to CTC-AE v4.03.

Exploratory objective: Quantifying Everolimus in the oral fluid of patients.

Study description

Background summary

The hypothesis of this study is that dosing everolimus 5mg twice daily(BID) instead of 10 mg once daily (QD) decreases the incidence of side effects, as a result of a lower Cmax while maintaining Cmin and AUC.
Everolimus is an effective oral drug with a sometimes challenging safety profile. In clinical practice a substantial number of patients has dose limiting or quality of life reducing side effects.

Some everolimus side effects (like stomatitis) may be Cmax driven. Stomatitis (any grade) occurs in more than half of all patients treated with 10 mg Everolimus QD. An incidence of 56% was reported in the BOLERO-2 trial by Baselga et al and 57% in a meta-analysis of oncology trials with everolimus in pNET, RCC, NSCLC and carcinoid by Raveaud et al. Grade 3-4 stomatitis occurred in 8% (Baselga et al) and 6% (Ravaud et al) of patients in these studies.

Considering the pharmacological properties of everolimus, we hypothesize that

this decrease in Cmax (while maintaining Cmin and AUC) can also be established by dividing the standard everolimus tablets over the day (upholding the same daily dose).

We suggest to perform a study measuring everolimus pharmacokinetics during twice daily dosing of 5 mg of standard everolimus tablets and compare this with PK data derived from once daily dosing of 10 mg of standard everolimus tablets. If the Cmax in the BID schedule is reduced whilst maintaining Cmin and AUC, spreading intake moments of everolimus over the day might reduce adverse events without compromising treatment efficacy.

Study objective

To describe and compare pharmacokinetics of everolimus in a 10 mg QD and everolimus 5mg BID schedule, evaluated PK parameters will be a.o. Cmax/Cmin ratio, AUC, Cmax, Cmin, Tmax.

Study design

Pharmacokinetic cross over trial of Everolimus 10 mg QD vs 5 mg BID.

Intervention

2 weeks of treatment with 5 mg BID Everolimus (+ 25 mg QD Exemestane).

Study burden and risks

Blood samples voor pharmacokinetic analysis and lab assessments (max 160 ml). Additional hospital visits (2 overnight stays and 2 outpatient visits).

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.Age >= 18 years;
2.Able and willing to give written informed consent;
3.Able and willing to undergo blood sampling for PK analysis;
4.Histopathologically confirmed advanced hormone positive, HER2 negative, breast cancer for which everolimus in combination with exemestane is considered standard of care.
5.Minimal acceptable safety laboratory values
a.ANC of >= 1.5 x 10^9 /L
b.Platelet count of >= 100 x 10^9 /L
c.Hepatic function as defined by serum bilirubin <= 1.5 x ULN, ASAT and ALAT <=2.5 x ULN
d.Renal function as defined by serum creatinine <= 1.5 x ULN or creatinine clearance >= 50 mL/min (by Cockcroft-Gault formula);

Exclusion criteria

1.Woman who are pregnant or breast feeding;
2.Known hypersensitivity to any of the study drugs or excipients;
3.Unable or unwilling to undergo pharmacokinetic sampling;
4.Use of any concomitant medication (including OTC and herbal medication) which may induce or inhibit function of CYP3A4, including but not limited to efavirenz, etravirine, nevirapine, rifampicine, boceprevir, claritromycine, elvitegravir, erytromycine, fluconazol, itraconazol, ketoconazol, posaconazol, telaprevir, verapamil, cyclosporine, voriconazol, dexamethason, St John*s Wort and grapefruit juice;
5.Patients with known alcoholism, drug addiction and/or psychiatric of physiological condition which in the opinion of the investigator would impair study compliance;
6.Evidence of any other disease, neurological or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for

treatment-related complications;
7.Legal incapacity

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-06-2015
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	Everolimus
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Aromasin
Generic name:	Exemestane
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	20-11-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-05-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-09-2015
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-004833-25-NL
CCMO	NL51475.031.14