An Open-label Single-arm Pharmacokinetic Trial, Investigating the Effect of CYP3A4 inhibitor Ritonavir on the Pharmacokinetics of Erlotinib

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Primary: 1. Effect of the highly potent CYP3A4 inhibitor ritonavir on the pharmacokinetics (PK) of erlotinib, measured as AUC0-24h, AUCmean, Cmax and CminSecondary objective 1. Safety of the CYP3A4 moderator ritonavir in combination with erlotinib,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON49212

Source
ToetsingOnline

Brief title
Pharmacokinetics of Erlotinib Plus Ritonavir

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, ono-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis

Source(s) of monetary or material Support: NKI-AvL

Intervention

Keyword: CYP3A4, Erlotinib, Pharmacokinetics, Ritonavir

Outcome measures

Primary outcome

the effect of the highly potent CYP3A4 inhibitor ritonavir on the

pharmacokinetics (PK) of erlotinib, measured as AUC0-24h, Cmax and Cmin.

Secondary outcome

1. The incidence and severity of adverse events of co-administration of the

highly potent CYP3A4 inhibitor ritonavir, according to CTC-AE v4.03.

2. To determine the correlation between the ritonavir pharmacokinetics

(AUC0-24h, Cmax and Cmin) and the incidence and severity of adverse events.

3. To Study the effect of the highly potent CYP3A4 inhibitor ritonavir on the

pharmacokinetics (PK) of the active metabolite of erlotinib OSI-420 , measured

as AUC0-24h, Cmax and Cmin.

4. Quantification of ctDNA, determined with Droplet digital PCR (ddPCR)

Study description

Background summary

The standard therapy for non-small cell lung cancer (NSCLC) has been chemotherapy for decades. By identification of oncogenic driver mutations in NSCLC, the treatment of this malignancy has been improved. The most common oncogenic drivers are epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ret proto-oncogene (RET) and receptor tyrosine kinase 1 (ROS1). These oncogenic drivers can be successfully treated by tyrosine kinase inhibitors (TKI). By identifying more (potential) driver genes, the increase in available TKI*s and the possibility for multiple treatment lines, the amount

of TKI use will keep rising in the coming years. Since the cost of this treatments will cover a large part of healthcare budget, new treatment strategies are needed to use TKI*s as effectively as possible. Currently, the knowledge about alternative treatment schemas is limited.

Erlotinib is a tyrosine kinase inhibitor(TKI), which inhibits the (activated mutated) epidermal growth factor receptor (EGFR). Erlotinib has several indications in e.g. non-small cell lung cancer (NSCLC) as maintenance therapy and in pancreatic cancer. In other tumortypes such as colorectal cancer and biliary cancer, EGFR overexpression may occur as well, indicating that erlotinib treatment in these cancers could be potentially therapeutic. There is a link between erlotinib exposure and toxicity. The link between the amount of exposure to erlotinib and response is not yet established.

Erlotinib is predominantly (~70%) metabolized by cytochrome P450 3A4 (CYP3A4), with CYP1A2 being responsible for the other *30%. Co-administration of the potent CYP-3A4 inhibitor ketoconazole increased the erlotinib exposure (AUC) and maximum concentration (Cmax) approximately by two-fold (mean ratio from 0.88 to 1.64, and 0.83 to 1.67, respectively), in healthy non-smoker males. Ciprofloxacin, an inhibitor of CYP3A4 and CYP1A2, co-administration resulted in an erlotinib AUC and Cmax increase of 39% and 17%, respectively.

Based on the above, the aim of this study is to investigate whether it is possible to decrease the dose of erlotinib when it is co-administrated with CYP3A4 inhibitor ritonavir. Also, this study will provide data about the pharmacokinetics of erlotinib with a highly potent CYP3A4 inhibitor ritonavir, which can be used as future guidance on dosing instructions and adverse events expectations when in daily care erlotinib is given to patients using a highly potent CYP3A4 inhibitor.

Study objective

Primary:
1. Effect of the highly potent CYP3A4 inhibitor ritonavir on the pharmacokinetics (PK) of erlotinib, measured as AUC0-24h, AUCmean, Cmax and Cmin

Secondary objective
1. Safety of the CYP3A4 moderator ritonavir in combination with erlotinib, which will be measured as the incidence and severity of adverse events with and without ritonavir, according to CTC-AE v4.03.
2. The correlation between the pharmacokinetics, measured as AUC0-24h, AUCmean, Cmax and Cmin of ritonavir and toxicity according to CTC-AE v4.03
3. Study the effect of the highly potent CYP3A4 inhibitor ritonavir on the pharmacokinetics (PK) of the active metabolite of erlotinib, OSI-420 , measured as AUC0-24h, AUCmean, Cmax and Cmin.

4. Quantification of ctDNA, determined with Droplet digital PCR (ddPCR)

Study design

This is a single-arm, open-label, pharmacokinetic trial. A schematic overview of the study is presented in figure 1. An overview of the study schedule is shown in Table 1. We will exam the effect of a highly potent CYP3A4 inhibitor ritonavir on the PK of erlotinib and thereby determine if it is possible to halve the dose of erlotinib by co-administration of CYP3A4 inhibitor ritonavir. All included patients are treated with single agent erlotinib 150mg QD for at least 4 weeks. At day 1 a PK measurement will take place (at steady state erlotinib 150mg QD). Since the half- life of erlotinib is 36 hours, steady state is reached with 5x36 = ~180 hours (7.5 days). Patients will start with erlotinib 75m QD at day 2 till day 8 of the study. From day 9 till day 15, patients will be treated with erlotinib 75mg QD + ritonavir 200mg QD. At day 15, a second PK measurement will take place. After day 15 patients will continue treatment of single agent erlotinib 150mg QD. Since there is no value of -and the potential risk of two CT-scans in one week, we do not perform response evaluation by CT-scan. Therefore, will monitor the mutation status in plasma ctDNA during treatment as surrogate response measurement.

Intervention

All subjects will receive erlotinib 75mg for 14 days. From 7 days, this will be combination with ritonavir for CYP3A4 inhibition.

Study burden and risks

There is a risk of additional toxicity, as we expect an increase in erlotinib exposure if taken combined with ritonavir. However, this risk is minimized by the short duration of the intervention (only seven days) and we halve the dose of erlotinib when it is combined with ritonavir.
Ritonavir has been administered to healthy volunteers up to oral doses of 600 mg at 12-hour intervals. Vomiting, nausea, and abdominal pain occurred frequently especially during the first few weeks of therapy, but only at the highest doses. These side-effects correlated with ritonavir plasma levels5. Since ritonavir in our study is administered at much lower doses and not as frequently as in the study reported in the literature performed in healthy volunteers, no serious side effects are expected from ritonavir in this study.
By halving the dosage, patients are temporary exposed to a lower dose of erlotinib. We do not expect this will be a problem, given the large therapeutic index of erlotinib.
Safety assessments, including measurement of vital signs, WHO performance status, hematology and clinical chemistry tests and toxicity assessments will be performed.
In our opinion, the remaining risks are acceptable for the subjects

participating in the study.

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

- Patients treated with single agent erlotinib 150mg QD, without disease progression at the first regular response evaluation after treatment initiation or patients who may benefit from erlotinib treatment.
- Age * 18 years
- Accessible for repeated venipunctures
- Ability to understand the study and give signed informed consent prior to beginning of protocol specific procedures

Exclusion criteria

- Concomitant use of medication(s) which could influence the pharmacokinetics of erlotinib 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
- Active uncontrolled infection or severe cardiac dysfunction (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina)
- Impaired hepatic function (total bilirubin > ULN or Child-Pugh A, B and C)
- Woman who are pregnant or breast feeding
- Progression on erlotinib at the latest regular response evaluation
- Current smokers

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-09-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Norvir
Generic name:	Ritonavir
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tarceva

Generic name:	Erlotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	28-01-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-04-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-06-2020
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2018-004854-12-NL
Other	N19RER
CCMO	NL68511.031.19

Study results

Date completed:	21-10-2021
Actual enrolment:	19