Pharmacokinetic boosting of osimertinib in patients with non-small cell lung cancer.

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

Summary

ID

NL-OMON55742

Source
ToetsingOnline

Brief title
OSIBOOST

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, lung carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Subsidie van ZonMW

Intervention

Keyword: Boosting, Cobicistat, NSCLC, Osimertinib

Outcome measures

Primary outcome

The main study parameter will be the change in exposure to osimertinib (i.e. AUC). The AUC of osimertinib will be measured at the start of the study (day 1) and after three weeks of co-treatment with cobicistat (day 22).

Secondary outcome

The Cmax of osimertinib and the safety and tolerability of the combination therapy will serve as secundary outcomes. Additionally, we will evaluate the genotype of CYP3A4 and CYP3A5 for participating patients.

Study description

Background summary

Multiple recently developed targeted agents have the potential to deliver benefit to cancer patients. However, the exorbitantly high prices of these new drugs threaten the financial sustainability of cancer treatment. Osimertinib is an example of such new anticancer agents. Like other new anticancer drugs, osimertinib is no exception in terms of high costs with annual drug costs of approximately ¤74,000 per patient.

In the pivotal randomized phase III study, osimertinib was significantly more effective than standard chemotherapy in patients with advanced epidermal growth factor receptor (EGFR) T790M-positive non-small cell lung cancer (NSCLC). The median progression free survival (PFS) in patients with progressive disease upon a first-line TKI was significantly longer with osimertinib than with a platinum-based therapy (10,1 vs. 4,4 months, $p < 0,001$). Therefore, osimertinib is registered as second-line treatment for these patients who progressed on first-line treatment with EGFR targeted tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib or afatinib.
Osimertinib has also been studied as first-line treatment in patients with EGFR-mutated NSCLC (exon 19 deletion or L858R). Osimertinib 80 mg was compared

to erlotinib 250 mg or gefitinib 150 mg. The PFS with osimertinib was significantly longer than with erlotinib/gefitinib (18,9 vs. 10,2 months, p < 0,001). Because of this, osimertinib has also been registered as first-line treatment for patients with EGFR-mutated NSCLC as mono therapy. The only remaining issue in the Netherlands is the reimbursement of osimertinib as first-line treatment for EGFR-mutated patients, which has not been approved until now.

The pharmacokinetic characteristics of osimertinib have been extensively studied. After multi-dose administration steady-state concentration is achieved by day 15. During steady-state the ratio between the maximal and minimal concentration osimertinib is 1.6 and the plasma-concentration curve is relatively flat due to the long half-time of osimertinib and the ratio for the minimal vs. maximal osimertinib concentration. Therefore, a low trough plasma concentration is a good reflection of an overall low exposure to osimertinib.

Osimertinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP3A5. As combined administration of osimertinib with a strong CYP3A4 inhibitor resulted in increased osimertinib exposure [8], the underlying mechanism of this drug-drug interaction may be used to boost osimertinib exposure in patients with relative low trough plasma concentrations in steady state (CminSS) without giving additional osimertinib.

Using this personalized treatment approach by implementing and combining the concepts of therapeutic drug monitoring (TDM) and pharmacokinetic boosting, osimertinib therapy could become much more cost-effective. By reducing the necessary dose of osimertinib, this strategy will ultimately result in a significant reduction in drug costs, as the additional expenditure for the CYP3A4 inhibitor and blood sample analysis are negligible compared to the price of osimertinib.
Cobicistat is a strong and selective CYP3A4 inhibitor. It is well known for its boosting capacity of HIV-drugs and recently it was successfully used to boost the exposure of axitinib, an anticancer TKI, in a patient with suboptimal exposure after receiving the standard dose. Therefore, together with low costs (¤1 per day) cobicistat is a suitable CYP3A4 inhibitor to investigate the boosting concept of osimertinib. Cobicistat by itself is not known for causing side-effects.

Study objective

The main objective of this study is to evaluate if systemic exposure of osimertinib (i.e. AUC) is enhanced when osimertinib is co-administered with cobicistat in patients with relatively low blood concentrations while receiving the standard osimertinib dose. Additionally the safety of combination therapy will be evaluated.

Study design

This is a prospective pharmacokinetic, proof-of-concept pilot-study, to evaluate to what extent cobicistat can increase the exposure to osimertinib. During the study the patients will be asked to visit the hospital twice and in between the two hospital-days the patient will use cobicistat for three weeks additional to the treatment with osimertinib.

The study will be planned as follows:
- Day 1: hospital-day, four blood samples taken right before the ingestion of osimertinib, and 0.5 - 1.5, 2.5 - 3.5 and 7-8 hours after ingestion of osimertinib. The blood samples will be taken using a intravenous canula.
- Day 2 - 22: additional treatment with cobicistat (150, 300 or 600 milligram).
- Day 22: hospital-day, same program as on day 1.

This study will not include a controlgroup or a placebo. Due to the nature of the study (proof-of-concept), the goal is that 20 patients will complete the study on the selected dosage. To achieve this, and to complete the dose-escalation part of cobicistat, and to compensate for withdrawal of patients, the goal is to include 29 patients in this study.

Patient can opt to continue with cobicistat in consultation with their treating physician, if the treatment was well tolerated during the first three weeks and increasing the dosage of cobicistat has been deemed as inappropriate, due to achieved effect and plasma concentrations of osimertinib. Patients that choose to continue treatment with cobicistat, are asked to undergo blood sampling, one more time to determine the plasma trough concentration of osimertinib to evaluate whether the effect of cobicistat is constant over time.

Intervention

The intervantion is the treatment with cobicistat 150/300/600 milligram additional to the regulare treatment with osimertinib.

Study burden and risks

Patients who experience plasma trough concentration of osimertinib below 195 ng/mL during steady state will be eligible to take part in this study. This plasma trough concentration is considerably lower than the mean measured in the two centres (224 ng/mL), but higher than the mean plasma through concentration reported in the literature (166 ng/ml). The discrepancy between the value reported in the literature and seen in the two centres can possible be explained: the results reported in the literature was from phase I and II clinical studies of osimertinib. Since then instability of osimertinib at room temperature and in the fridge was reported. To prevent degradation it is necessary to take precautionary measures, such as storage at -80 degrees

Celsius and the use of dry-ice during transport. We believe that it is plausible that not all precautionary measures were taken for transport and storage of all blood samples in the phase I and II samples. Therefore, we decided to relate the threshold value for the plasma through concentration of osimertinib on the mean concentration in the two centres, in stead of the value reported in the literature.

This low plasma trough concentration of osimertinib could possibly result in suboptimal treatment-outcomes with osimertinib. Although such an relation between exposure and effectiveness of the treatment with osimertinib, this could lead to better treatment outcomes in those patients. A disadvantage of the increase in osimertinib exposure is the possibility to experience adverse events, which are common with osimertinib. Those adverse events could have been absent prior to the start of the study. The estimation is that the adverse events will be mild. In the registration study patients treated with osimertinib experienced relatively few adverse events, which were mainly CTCAE grade 2 or lower.

The main burden during the study will be the two days in the hospitals, for which the amount of time spent in the hospital will be the primary burden. During the two days in the hospital the patients will have to spend 7 - 8 hours in the hospital, but will not be bedridden during those days. For research purposes a intravenous cannula will be placed, which will be used to draw a small amount of blood (four times) during the day. As a study-visit will be combined with a routine-visit and therefore no additional punctures will be needed to draw blood.

In conclusion, we think that the risk of this study is limited. The adverse events which could be experienced by the participating patients are already common for osimertinib and will be recognized by the treating physicians. Besides, the patient will experience little physical discomfort for this 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 with EGFR-mutated NSCLC receiving standard treatment with osimertinib for at least 2 months (steady-state) without any signs of disease progression, or during treatment beyong progression, if treatment for another couple of months is expected. After anticipated EMA approval of osimertinib adjuvant therapy, patients on adjuvant osimertinib treatment may also participate on the following conditions: if they are receiving standard treatment with osimertinib for at least 2 months (steady-state), and if treatment will be continued for a longer period than necessary for participation in the OSIBOOST-trial.
- Patients with osimertinib plasma trough concentration below 195 ng/ml.
- Age * 18 years
- WHO performance status * 2.
- Able and willing to give written informed consent.
- Able and willing to undergo blood sampling for pharmacokinetic analysis.

Exclusion criteria

- Any concurrent medication that is known to strongly inhibit or induce CYP3A4.
- Refusing to retain from consuming CYP3A4-influencing products, such as St John's wort or grapefruitjuice).
- Pregnancy of breast feeding.

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):	26-11-2020
Enrollment:	29
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tybost
Generic name:	Cobicistat
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	26-04-2019
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	03-07-2019
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	02-11-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-11-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-06-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-06-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2018-004290-28-NL
ClinicalTrials.gov	NCT03858491
CCMO	NL68172.068.19