Trastuzumab-emtansine and osimertinib combination treatment to target HER2 bypass track resistance in EGFR mutation positive NSCLC

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-To dertermine the objective response rate (ORR) and disease control rate (DCR) (according to RECIST v1.1) after 3 months of treatment with T-DM1 and osimertinib in patients with EGFR mutation positive NSCLC and HER2 bypass track activation-To...

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

Summary

ID

NL-OMON55787

Source
ToetsingOnline

Brief title
TRAEMOS

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis

Source(s) of monetary or material Support: Astra Zeneca,farmaceutische industrie: Astra Zeneca en Roche RRG,Roche RRG

Intervention

Keyword: HER2, non-small cell lung cancer, osimertinib, trastuzumab-emtansine

Outcome measures

Primary outcome

-Objective response rate, ORR, (according to RECIST v1.1) after three months of

treatment course with T-DM1 and osimertinib

Secondary outcome

-Safety as indicated by intensity and incidence of adverse events, graded

according to NCI CTC AE 4.03

-Objective tumorresponse (CR and PR), according to RECIST v1.1

-Duration of response, according to RECIST v1.1

-Progression-free survival, defined as the interval between initiation of study

treatment and the date of radiological progression, determined by RECIST 1.1 or

death

-Overall survival, defined as the interval between initiation of study

treatment and the date of death

Study description

Background summary

Patients with epidermal growth factor receptor (EGFR) mutation positive non-small cell lung cancer (NSCLC) respond well to EGFR TKI treatment. However, despite this high response rate resistance develops in every patient. Multiple resistance mechanisms have been described, involving two main mechanisms: EGFR alteration and bypass track activation. Two in vivo studies detected human

epidermal growth factor receptor 2 (HER2)-overexpression and amplification in ~15% of NSCLC-patients with acquired tyrosine kinase inhibitor (TKI)-resistance. Recently we showed that targeting HER2 with trastuzumab and paclitaxel in this setting can induce tumor responses in up to 46%. However, the progression-free survival was rather disappointing, which seems to be caused by tumor escape through EGFR signaling and limited efficacy of trastuzumab-paclitaxel in the brain. Isolated brain progression with a partial response of the extra cerebral disease or a sudden disease flare caused by EGFR TKI discontinuation were present in 25% of the patients, suggesting that co-inhibition of EGFR and HER2 might be advantageous. Another question remains about the optimal HER2 targeting regimen in this setting.
Trastuzumab-emtansine (T-DM1) is a HER2 antibody-drug conjugate that releases a cytotoxic anti-microtubule agent within HER2 positive tumor cells upon degradation of the HER2-T-DM1 complex in lysosomes. In-vitro experiments suggest that T-DM1 can overcome HER2 bypass track resistance in patients with EGFR mutated NSCLC. In addition, T-DM1 has shown in patients with breast cancer that the efficacy is equivocal to paclitaxel and trastuzumab and that T-DM1 can be used as a taxane-free treatment regimen with less toxicity.
In the current study we will evaluate whether combination treatment with T-DM1 and the 3rd generation EGFR TKI osimertinib can improve the results that were obtained in our previous trial and whether this HER2 targeting regimen can be put forward in a randomized phase III trial against standard of care treatment.

Study objective

-To dertermine the objective response rate (ORR) and disease control rate (DCR) (according to RECIST v1.1) after 3 months of treatment with T-DM1 and osimertinib in patients with EGFR mutation positive NSCLC and HER2 bypass track activation
-To assess anti-tumor activity of T-DM1 and osimertinib (the disease controle rate (DCR), progression free survival (PFS), overall survival (OS)) in the HER2 expression and amplification subgroups
-To evaluate the safety of the combination treatment with T-DM1 and osimertinib
-At baseline and at progression, tumorbiopsies will be analysed for mechanisms of de-novo and acquired resistance
-At baseline, during treatment and at progresssion, cfDNA will be collected to analyse possible resistance mechanisms

Study design

Single arm, open label, multicenter fase II study

Intervention

All subjects will receive continuous daily treatment with osimertinib 80 mg once daily and 3.6mg/kg T-DM1 i.v. tri-weekly until disease progression or

unacceptable toxicity.

Study burden and risks

The disadvantage of participating in this study is that more blood will be taken than normal. A new screening biopsy could also be taken if there is no adequate tumor material available. A biopsy may possibly cause bleeding, low blood pressure, redness, bruising, swelling and/or infection at the site of biopsy or other discomfort such as bruising feeling.
The anesthetic may possibly cause allergic reaction. At the site where the biopsy is performed a scar can occur. If a tumor is punctured in the lung, a collapsible lung may develop. The patients all get osimertinib and T-DM1 and can suffer from the most side effects.

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

-Histologically or cytologically confirmed stage IV non-squamous NSCLC, characterized by an activating EGFR mutation., -Progressive disease according to RECIST 1.1 on first, second or third generation EGFR TKI and still receiving the drug., -A rebiopsy after having acquired resistance to a first, second or third generation TKI-treatment must have been performed and be:, a. Negative for T790M in case of treatment with a first or second generation EGFR TKI. After progression on a third generation EGFR TKI patients may either be positive or negative for T790M., b. Positive for HER2-overexpression (positive membranous immunohistochemistry staining IHC >=2+ (on a scale of 0-3) in >=10% of the cells) must have been detected., -There must be at least one measurable disease site, according to RECIST 1.1 criteria., -Absence of symptomatic brain metastases. All patients will be scanned at baseline with a brain MRI., -Patients must be willing and able to comply with the protocol for the duration of study including undergoing treatment and scheduled visits and examinations., -World Health Organization (WHO) performance status 0-2., -Patients must have a life expectancy >=12 weeks., -Ability to give written informed consent before patient registration., -Patients must be >=18 years of age., -Men and women of child bearing potential should be willing to take adequate contraceptive measures during the study and until three months after study drug discontinuation.

Exclusion criteria

-Uncontrolled infectious disease., -Other active malignancy., -Major surgery (excluding diagnostic procedures like e.g. mediastinoscopy or VATS biopsy) in the previous 4 weeks., -Known hypersensitivity to T-DM1 or osimertinib (or drugs with a similar chemical structure or class) or any excipients of these agents., -Previous treatment with a HER2 monoclonal antibody., -Clinically significant cardiac disease or a Left Ventricular Ejection Fraction (LVEF) of <40%., -Inadequate bone marrow reserve or organ function, as demonstrated by any of the following laboratory values: Haematology: haemoglobin <5.6mmol/L, absolute neutrophil count <1.5 x 10^9/L, platelet count <100 x 10^9/L. Biochemistry: alanine aminotransferase, aspartate aminotransferase and bilirubin <= 3x ULN, except in the case of liver metastases where these values must be <= 5x ULN. Creatinine clearance <50 ml/min (measured or calculated by Cockroft and Gault equation)., -Patients with symptomatic central nervous system metastases who are neurologically unstable., -Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow osimertinib or previous significant bowel resection that would preclude adequate resorption of osimertinib., -Patients on anticoagulant treatment will not be excluded, but should be monitored closely during T-DM1 treatment., -Males and females of reproductive potential who are not using an effective method of birth control

and females who are pregnant or breastfeeding or have a positive (serum) pregnancy test prior to study entry., -Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-01-2019
Enrollment:	58
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kadcyla
Generic name:	Trastuzumab-emtansine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tagrisso
Generic name:	Osimertinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-08-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	07-12-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-09-2021
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	EUCTR2018-002885-38-NL
CCMO	NL66662.031.18

Study results

Summary results

Trial ended prematurely