A multicentre single-arm phase II trial assessing the safety and efficacy of first-line osimertinib and locally ablative radiotherapy in patients with synchronous oligo-metastatic EGFR-mutant non-small cell lung cancer

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Respiratory and mediastinal neoplasms benign (excl mesotheliomas)
Study type	Interventional

Summary

ID

NL-OMON54434

Source
ToetsingOnline

Brief title
17-20 STEREO

Condition

- Respiratory and mediastinal neoplasms benign (excl mesotheliomas)

Synonym
lungcancer, Non small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: ETOP IBCSG Partners Foundation
Source(s) of monetary or material Support: Astra Zeneca,ETOP IBCSG Partners

Intervention

Keyword: EGFR mutation (exon 19 deletion and/or exon 21 L858R), NSCLC, Osimertinib, SBRT

Outcome measures

Primary outcome

- Proportion of patients with grade >=2 pneumonitis, requiring medical

treatment, by

month 18

- Hierarchically tested: Progression-free survival

Secondary outcome

- Overall survival

- Pattern of disease progression

- Distant progression free survival

- Objective response rate

- Duration of response

- Adverse events according to CTCAE v5.0

- Symptom-specific and global quality of life

Study description

Background summary

Targeting EGFR mutation has fundamentally changed the treatment of metastatic NSCLC.
Several randomised phase III studies have compared first-generation (erlotinib or gefitinib) or
second-generation (afatinib) EGFR-targeting TKIs with standard platinum-based chemotherapy and all reported significantly improved objective response rates (ORR) and
progression-free survival (PFS). For patients with TKI resistance development by T790M mutation, which is the resistance mechanism in about 50% of the patients, osimertinib
is superior compared to platinum-based chemotherapy with significant and clinically relevant
improved ORR and PFS. On longer follow-up, first-line osimertinib was also associated with improved survival.
Integration of local therapy into a multimodality treatment is a promising strategy to overcome
the limitations of EGFR-targeting TKIs alone, despite patients suffering from a metastatic
stage of disease. This is based on the observations that disease progression under EGFR targeting TKI most frequently occurs at the original sites of metastatic disease and that the majority of patients show disease progression in a limited number of metastatic lesions, a
situation defined as oligoprogression. Early imaging-based detection of oligoprogressive disease sites and their local ablation
combined with continuation of TKI is one strategy to overcome this resistance development:
metastatic sites with acquired resistance to EGFR-targeting TKI are eradicated by locally
ablative treatment, irrespective of the underlying resistance mechanism, whereas nonprogressing and EGFR-sensitive sites are continuously targeted and controlled by TKI therapy. There is a clinical need to evaluate locally ablative therapy in oligo-metastatic EGFR-mutant NSCLC patients and simultaneously a strong rationale that this population might benefit in particular from a combined modality treatment: the benefit of locally ablative therapy is expected to be largest in situations of effective systemic therapies to control locally untreated microscopic disease which is true for EGFR targeting.

Study objective

The objective of this trial is to evaluate safety (in terms of grade >=2 pneumonitis, requiring
medical treatment) and efficacy (in terms of PFS) in patients with synchronous oligometastatic EGFR-mutant NSCLC treated with osimertinib and locally ablative radiotherapy
to all cancer sites

Study design

Single-arm, multicentre phase II trial evaluating the safety (in terms of grade >=2 pneumonitis, requiring medical treatment) and efficacy (in terms of progression-free survival) of osimertinib and locally ablative stereotactic radiotherapy in patients with synchronous oligo-metastatic EGFR-mutant NSCLC.

Intervention

All patients will be treated with Osimertinib, 80 mg once daily p.o., until progression or unacceptable toxicity. Locally ablative radiotherapy (SBRT) will be delivered to the primary tumour and to all metastatic sites. SBRT will be delivered using risk-adapted SBRT with a maximum of 5 SBRT fractions. Depending on tumour size and anatomical location in relationship to critical serial organs at
risk, SBRT will either be delivered immediately (SBRT to start within 4 weeks after start of
osimertinib treatment) or after the 2-month restaging (SBRT to start within 4 weeks after
restaging).
The decision when to start SBRT is at the discretion of the local radiotherapy team.

Furthermore, the following study procedures/assessments will be performed: medical examination (measurement of body weight, temperature, pulse, blood pressure and checking the eyes for redness and other symptoms), general well-being questions to determine performance or activity level, blood and urine tests, cardiac function tests (ECG and LVEF), quality of life questionnaires, radiologic scans (FDG-PET-CT, MRI and CT), lung cancer biopsy (if disease progression).

Study burden and risks

The study procedures and tests can be found in the protocol (pages 19-21).

- Possible side effects of osimertinib: Sudden difficulty in breathing along with a cough or fever ('interstitial lung disease'), watery eyes, sensitivity to light, eye pain, red eyes, or vision changes, ring-shaped skin reactions, Stevens-Johnson syndrome (reddish flat dots or round spots, often with a central blister on the body, peeling skin, ulcers of the mouth, throat, nose, genitals and eyes You may also develop fever and flu-like symptoms, diarrhea, skin and nail problems, stomatitis, decline of white blood cell count, anaemia, inflammation of the blood vessels in the skin, decrease of red blood cell production (aplastic anaemia).

- Possible side effects of radiation therapy: fatigue, shortness of breath and dry cough, nausea and vomiting, temporary worsening of the original symptoms, skin changes on the treated areas, hair loss (temporary/permanent), diarrhea, difficulty swallowing or pain when swallowing, chest pain / fractured rib (bone fractures in other treated areas), impaired / limited breathing ability, liver dysfunction, renal dysfunction, low risk of major bleeding/delayed swallowing difficulties/bowel damage/damage to heart function/nerve damage/spinal cord damage

- Blood samples can hurt or cause a blood shed. This may increase the risk of infection.

- There is a risk of an allergic reaction in radiological examinations that require injection of a contrasting agent.

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) Histologically confirmed, treatment naïve EGFR-mutant NSCLC, with or without T790M resistance mutation.
2) Presence of sensitising EGFR-mutation (exon 19 deletion and/or exon 21 L858R) detected by an accredited laboratory.
3) Synchronous oligo-metastatic stage IV disease (max 5 lesions)
4) Measurable disease as defined according to RECIST v1.1
5) All lesions amenable for radical radiotherapy according to local judgment
6) ECOG performance status 0-2
7) Adequate haematological, renal and liver function

Exclusion criteria

1) Prior chemotherapy, immunotherapy, radiotherapy or therapeutic surgery for NSCLC (an exception is the resection and postoperative radiotherapy of the resection cavity of CNS or adrenal metastases)
2) More than 5 distant oligo-metastases (any second intra-thoracic lesion will count as a distant metastasis; regional nodal metastases will not count towards the 5 oligometastases) and more than 2 intra-pulmonary lesions.
3) Brain metastases not amenable for radiosurgery or neurosurgery
4) Presence of leptomeningeal metastases
5) Symptomatic spinal cord compression
6) Extracranial metastatic locations not amenable for radical radiotherapy such as malignant ascites, pleural or pericardial effusion, diffuse lymphangiosis of skin or lung, diffuse bone marrow metastasis, metastasis invading the GI tract, abdominal masses/abdominal organomegaly, identified by physical exam that is not measurable by reproducible imaging techniques
7) Currently receiving, or unable to stop use prior to enrolment or to receiving the first dose of osimertinib treatment, medications or herbal supplements known to be potent CYP3A4 inducers. Potent CYP3A4 inducers are contraindicated for the duration of the trial.
8) Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol.
Patients with a resolved or chronic HBV infection are eligible if they are:
- Negative for HBsAg and positive for hepatitis B core antibody [anti-HBc IgG],
or

- Positive for HBsAg, negative for HBeAg but for >6 months have had transaminases levels below ULN and HBV DNA levels below 2000 IU/mL (i.e., are in an inactive carrier state).
9) Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib
10) Any of the following cardiac criteria:
- QTcF >470 msec, using the screening clinic ECG machine derived QTc value (QTcF: corrected QT interval using Fredericia's formula).
- Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block or
second degree heart block).
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medication known to prolong the QT interval and cause Torsades de Pointes (TdP).
11) Past medical history of ILD, drug induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD
12) Idiopathic pulmonary fibrosis which is a contraindication to lung radiation
13) History of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib

Study design

Design

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

Recruitment

NL
Recruitment status:	Will not start
Enrollment:	10

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Tagrisso
Generic name:	Osimertinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-03-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	23-06-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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	EUCTR2020-004114-35-NL
ClinicalTrials.gov	NCT04908956
CCMO	NL79320.058.22