RANDOMIZED, OPEN LABEL, MULTICENTER, PHASE III STUDY OF ENTRECTINIB VERSUS CRIZOTINIB IN PATIENTS WITH LOCALLYADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER HARBORING ROS1 GENE REARRANGEMENTS WITH AND WITHOUT CENTRAL NERVOUS SYSTEM METASTASES

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This study has been transitioned to CTIS with ID 2023-507494-18-00 check the CTIS register for the current data. This study will evaluate the efficacy and safety of entrectinib compared with crizotinib in patients who have NSCLC harboring ROS1 gene...

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

Summary

ID

NL-OMON54429

Source
ToetsingOnline

Brief title
MO41552

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
lung cancer, Non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: Crizotinib, Entrectinib, NSCLC, ROS1 mutation

Outcome measures

Primary outcome

To evaluate the efficacy of entrectinib compared with crizotinib in patients

who have ROS1 rearrangement-positive NSCLC with CNS metastases at baseline

The corresponding endpoint: Progression-free survival (PFS), defined as the

time from randomization to the first documented disease progression

(extracranial or intracranial) or death from any cause, whichever occurs first,

as determined by a blinded independent review committee (BIRC) using RECIST

v1.1

Secondary outcome

Evaluate the efficacy of entrectinib compared with crizotinib in patients who

have ROS1 rearrangement-positive NSCLC in the whole study population (ITT).

Evaluate the efficacy of entrectinib compared with crizotinib in patients who

have ROS1 rearrangement-positive NSCLC with CNS metastases at baseline

Evaluate the efficacy of entrectinib compared with crizotinib in patients who

have ROS1 rearrangement-positive NSCLC in the whole study population (ITT)

Evaluate the efficacy of entrectinib compared with crizotinib in patients who

have ROS1 rearrangement-positive NSCLC with CNS metastases at baseline

Evaluate the safety of entrectinib compared with crizotinib in patients who

have ROS1 rearrangement-positive NSCLC

To evaluate the tolerability of entrectinib compared with crizotinib from the

patient's perspective

Corresponding endpoints are described in section 2 of the protocol.

Study description

Background summary

Lung cancer is the leading cause of cancer incidence and mortality worldwide.
The primary form of lung cancer is non-small cell lung cancer (NSCLC), which occurs in approximately 85% of all lung cancer cases.
Prognosis is typically poor in NSCLC patients with brain metastases. An important unmet clinical need exists for new systemic agents that effectively and safely treat CNS metastases in patients with advanced cancers.
Approximately 1 to 2% of patients with NSCLC harbor gene rearrangements between the ROS proto-oncogene 1, receptor tyrosine kinase (ROS1) oncogene.
Crizotinib was the first RTK inhibitor with demonstrated activity against ROS1 to be approved.
Entrectinib (also known as RXDX-101) is a potent, oral, small-molecule inhibitor of the tyrosine kinases ROS1.
Data provided in studies (described in the protocol) support the hypothesis that entrectinib may have higher CNS activity against ROS1

rearrangement-positive NSCLC than crizotinib, which could be of highly significant clinical importance given the poor outcomes of patients who have brain metastases in this setting. To test this hypothesis, the primary endpoint of the current Phase III trial will directly compare the efficacy and safety of entrectinib versus crizotinib in patients with advanced or metastatic ROS1 rearrangement-positive NSCLC who have CNS disease at baseline.

Study objective

This study has been transitioned to CTIS with ID 2023-507494-18-00 check the CTIS register for the current data.

This study will evaluate the efficacy and safety of entrectinib compared with crizotinib in patients who have NSCLC harboring ROS1 gene rearrangements with and without CNS metastases. Specific objectives and corresponding endpoints for the study are outlined in protocol section2.

Study design

Study MO41552 is a randomized, open-label, multicenter, Phase III trial. The study will consist of a 28-day Screening Period, a Treatment Period, a Post-Treatment Follow-Up Visit occurring 4 weeks after the end of study treatment, and a Follow-Up Period. For each participating patient, the first day of treatment will be Day 1 (baseline). The overall study design is presented in Figure 1 of the Protocol.

Intervention

The investigational medicinal products (IMPs) for this study are entrectinib and crizotinib.
In section 4.3 of the protocol more information is described about the Study Treatment, Dosage and Administration

Study burden and risks

The general burden for the patient consists of (a.o.) the withdrawal of blood samples, possible collection of tumor sample,
administration of investigational products which may lead to various adverse events. These are described in the Investigators' Brochure (Entrectinib) and in the SmPC Crizotinib.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

•Age >= 18 years
•Histologically- or cytologically-confirmed diagnosis of advanced or recurrent (Stage IIIB/C, not amenable for radical treatment) or metastatic (Stage IV) NSCLC that harbors a documented ROS1 gene rearrangement
•No prior treatment with a ROS1 tyrosine kinase inhibitor, chemotherapy or other systemic therapy for advanced or recurrent (Stage IIIB/C not amenable for radical treatment) or metastatic (Stage IV) NSCLC
•Prior radiotherapy is allowed if more than 14 days have elapsed between the end of treatment and randomization. Patients who received brain irradiation must have completed whole brain radiotherapy at least 14 days prior and/or stereotactic radiosurgery at least 7 days prior to the start of entrectinib treatment
•Measurable systemic disease according to RECIST v1.1
•Patients with measurable and non-measurable CNS lesions per RECIST v1.1, including leptomeningeal carcinomatosis, are eligible, provided that the patient is neurologically stable for at least 1 week prior to the first dose of study treatment

•Life expectancy of at least 12 weeks
•Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2
•Adequate hematologic, renal, liver function
• Recovery from effects of any major surgery or significant traumatic injury at least 28 days before the first dose of study treatment
• Ability to comply with the study protocol, in the investigator*s judgment
• Ability to swallow entrectinib and crizotinib intact without chewing, crushing, or opening the capsules
• For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined in the protocol

•For men: agreement to remain abstinent or use contraceptive measures, and agreement to refrain from donating sperm

Exclusion criteria

•Current participation in another therapeutic clinical trial
•Prior treatment with a ROS1 tyrosine kinase inhibitor, chemotherapy or other systemic therapy for advanced or recurrent (Stage IIIB/C not amenable for radical treatment) or metastatic (Stage IV) NSCLC
•NCI-CTCAE v5.0 Grade 3 or higher toxicities due to any prior therapy (excluding alopecia, fatigue, nausea and lack of appetite), which have not shown improvement and are strictly considered to interfere with current study medication
•History of recent (within the past 3 months) symptomatic congestive heart failure or ejection fraction <= 50% observed during screening for the study
•History of prolonged QTc interval
•History of additional risk factors for torsades de pointes
•Peripheral sensory neuropathy >= Grade 2
•Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis
•Previous malignancy within the past 3 years (other than curatively treated basal cell carcinoma of the skin, early gastrointestinal (GI) cancer by endoscopic resection, in situ carcinoma of the cervix, or any cured cancer that is considered to have no impact on PFS and OS for the current NSCLC)
•Incomplete recovery from any surgery prior to the start of study treatment that would interfere with the determination of safety or efficacy
•Active GI disease or other malabsorption syndrome that would reasonably impact drug absorption
•History of prior therapy-induced pneumonitis
•Any condition (in the past 3 months) that would interfere with the determination of safety or efficacy of study treatments
•Known active infections that would interfere with the assessment of safety or efficacy of study treatments (bacterial, fungal or viral, including human

immunodeficiency virus positive)
•History of hypersensitivity to any of the additives in the entrectinib and/or crizotinib drug formulations
• Pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of entrectinib or crizotinib
• HIV-positive patients may be enrolled, unless these patients meet any of the riteria stated in the protocol

•Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or the absorption of oral medications or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the patient in this study
•Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures; those conditions should be discussed with the patient before trial entry

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-11-2021
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rozlytrek
Generic name:	Entrectinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xalkori
Generic name:	Crizotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-07-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-09-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	24-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EU-CTR	CTIS2023-507494-18-00
EudraCT	EUCTR2019-003859-11-NL
ClinicalTrials.gov	NCT04603807
CCMO	NL76805.056.21