A phase III, randomized, controlled, open-label, multicenter, global study of capmatinib versus SoC docetaxel chemotherapy in previously treated patients with EGFR wt, ALK negative, locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC harboring MET exon 14 skipping mutation (MET*ex14)

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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-OMON52922

Source
ToetsingOnline

Brief title
CINC280A2301 - capmatinib in EGFR-wild, ALK-neg, MET exon14skip NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
non small cell lung cancer with a C-MET mutation

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor van dit onderzoek)

Intervention

Keyword: Capmatinib, docetaxel, INC280, MET, NSCLC

Outcome measures

Primary outcome

To compare the efficacy of capmatinib versus docetaxel by blinded independent review committee (BIRC)-confirmed progression free survival as per RECIST 1.1.

Secondary outcome

* To assess the antitumor activity of capmatinib versus docetaxel by evaluating duration of response (DOR), time to response (TTR) and disease control rate (DCR), all calculated per RECIST 1.1, both by BIRC and investigator.
Additionally the overall response rate (ORR) and progression free survival as per RECIST 1.1 as calculated by the investigator.

* To evaluate overall survival (OS) in participants treated with capmatinib versus docetaxel

* To evaluate the safety profile of capmatinib versus docetaxel by the incidence of adverse events, change in vital signs, laboratory results and ECG.

* To characterize the pharmacokinetics of capmatinib in this study population.

* To assess the effect of capmatinib versus docetaxel on patient-reported

questionnaires by changes of baseline in European Organization for Research and Treatment of Cancer (EORTC) QLQ-LC13, QLQ-C30, EuroQoL-5 Dimension-5 Level/EQ-5D-5L) questionnaires and time to symptom deterioration for chest pain, cough and dyspnea in the European Organization for Research and Treatment of Cancer (EORTC) QLQ-LC13 as well as global health status/QoL per QLQ-C30 questionnaire

* To assess intracranial anti-tumor activity of capmatinib and docetaxel in participants with Central Nervous System (CNS) lesions at baseline by BIRC assessed Overall intracranial response rate (OIRR), duration of intracranial response (DOIR), time to intracranial response (TTIR), intracranial disease control rate (IDCR) as per RANO-BM criteria.

Study description

Background summary

Lung cancer represents 11.6% of all new cancers and 85% of these lung cancers are defined as non-small cell lung cancers (NSCLC). Deciphering the oncogenisis of lung cancer have revealed various oncogenic drives, with mutations in EGFR & ALK rearrangements as the most common once. Various therapeutic strategies have been designed to inhibit the signaling pathways of these oncogenic drivers.
MET is a receptor tyrosine kinase involved in embryogenesis, organogenesis and tissue damage repair and MET dysregulation has been shown to be oncogenic, promoting cell-cell detachment and metastasis, epithelial-mesenchymal transition, invasion, angiogenesis, proliferation and survival. MET dysregulation is considered a poor prognostic factor.
Capmatinib (INC280) is a small adenosine triphosphate (ATP) competitive, orally bioavailable, highly potent, and selective reversible inhibitor of the MET receptor tyrosine kinase. Clinical data demonstrate that capmatinib monotherapy has anti-tumor activity in EGFR wild-type NSCLC harboring MET mutation and Safety data demonstrate that capmatinib is well tolerated by the target population at the recommended phase II dose of 400 mg b.i.d. (tablet).

Study objective

In this study, we want to find out whether the new drug capmatinib is more effective (i.e. better inhibits the growth of cancer cells) than the widely used chemotherapy docetaxel. In addition, it will be assessed whether treatment with capmatinib is sufficiently safe. The effects of capmatinib and docetaxel will be compared.
The research will be carried out in patients with locally advanced or metastatic NSCLC with a mutation of the MET gene in the so-called exon 14. Exon 14 is a specific part of the gene. These patients should not have mutations of other genes (EGFR gene and ALK gene) and must have been previously treated for their NSCLC.
It is also assessed how much capmatinib remains in the blood and how long it remains in the blood.
Research is also being conducted into biomarkers. Biomarkers are body substances, usually proteins or genes, that say something about the progress of the disease and the influence of research treatment on it.

Study design

This is a multicenter, open-label, randomized, active-controlled, global phase III study. The study will randomize approximately 90 participants globally. Participants eligible for the study will be randomized in a 2:1 ratio to one of the two treatment arms: capmatinib (investigational therapy) or docetaxel. The randomization will be stratified by prior lines of systemic therapy received for advanced/metastatic disease (one line vs. two lines).
Participants randomized to docetaxel treatment will be eligible to crossover to receive capmatinib treatment after blinded independent review committee (BIRC)-confirmed, RECIST 1.1-defined progressive disease (PD) and after meeting the eligibility criteria.
For all participants, the respective treatment (either with capmatinib or docetaxel) may be continued beyond initial disease progression as per RECIST 1.1 (as assessed by the investigator and confirmed by BIRC) if, in the judgment of the investigator, there is evidence of clinical benefit, and the participant wishes to continue on the study treatment.
After treatment discontinuation, all participants will be followed for safety evaluations during the safety follow-up period, and the participant*s status will be collected every 12 weeks as part of the survival follow-up.

Intervention

Treatment with INC280 (capmatinib)

Study burden and risks

Risks are possible adverse events of the study medication and study tests. Not all side effects of the study medicines are known at this time.
Participation in the study also means that patients need to invest time, will

have additional tests and need to adhere to agreements.

Possible side effects of capmatinib:
* Very common side effects (affecting at least 1 in 10 people): Abnormal physical weakness and/or lack of energy/tiredness (asthenia or fatigue), back pain, chest pain (unrelated to heart), constipation, cough, decrease in blood albumin level, decreased appetite, diarrhea, fever (pyrexia), nausea, possible signs of kidney dysfunction (blood creatinine increased), possible signs of liver dysfunction/changes in liver function tests (blood transaminase (ALT) increased), shortness of breath, swelling in arms and legs (peripheral edema), vomiting, weight decreased
* Common side effects (affects 1 in 10 to 100 people): Sudden decline in kidney function (acute kidney injury), bacterial skin infection with redness of the skin (cellulitis), decrease in blood mineral levels involved in body functions (phosphate, sodium), inflammation of lung tissue (pneumonitis/interstitial lung disease), possible signs of liver dysfunction/changes in liver function tests (blood bilirubin increased, transaminase (AST) increased), possible signs of pancreatic dysfunction/pancreatic enzymes increased (amylase and/or lipase), raised itchy bumps/hives (urticaria), skin itching
* Unusual side effects (affects 1 in 100 to 1,000 people): Sudden painful inflammation of the pancreas (acute pancreatitis).
* Other possible side effects of Capmatinib:
o Pneumonitis or interstitial lung disease has been reported during studies with capmatinib. Until now, the contribution of capmatinib to these events has not been proven.
o In animal experiments, capmatinib caused skin sensitization to sunlight, therefore you may sunburn more easily.
o In addition, based on the way capmatinib works and based on information from animalexperiments, it is highly likely that capmatinib can cause malformation in fetuses if it is taken during pregnancy.

Possible side effects of docetaxel:
* Very common side effects (affects 1 in 10 people or more): Infections, decrease in white blood cells (neutropenia), decrease in red blood cells (anemia), decrease in platelets (thrombocytopenia), decreased appetite (anorexia), damage to peripheral nerves (peripheral sensory neuropathy), nausea, sores in the mouth (stomatitis), vomiting, diarrhea, hair loss (alopecia), skin reaction, pain, feeling of weakness (asthenia), fluid retention.
* Common side effects (affects 1 in 10 to 100 people): Fever with dangerously low white blood cell count (febrile neutropenia), hypersensitivity, blood pressure decreased (hypotension), irregular heartbeats (arrhythmia), damage to peripheral nerves (peripheral motor neuropathy), nail disorders, constipation, muscle pains (myalgia), possible signs of liver dysfunction/changes in liver function tests (blood bilirubin increased).

The examination tests are one of the usual medical tests. Discomforts of research tests and procedures can be experienced.
* Blood samples: The risks of collecting blood may include fainting, pain, bruising, and/or dizziness, and in rare cases, infection. Rarely, there may be a small blood clot or infection at the site of the needle puncture or central line.
* Tumor biopsy: In general, having a biopsy can cause pain, swelling, bleeding and/or infection at the site where the biopsy needle penetrates through your skin. If your Study Doctor decides to use anesthetic, an allergic reaction may occur. There is also the possibility that having this procedure may shift some cells from the tumor into the surrounding tissues.
* CT or PET scan: With a CT or PET scan, the patient will be exposed to radiation, about the same as what we are exposed to in daily life in 2 to 10 years. Radiation can cause damage to genetic material. Some people experience claustrophobia (fear in a small space). You will receive an injection of contrast fluid before the scan. This may result in some nausea, fainting, pain, feeling of heat, swelling, bruise, scab or infection. Occasionally an allergic reaction to the contrast medium occurs with hot flashes, sweats, rashes, breathing problems and nausea. A serious allergic reaction can be life threatening.
* MRI scan: Some people experience claustrophobia. You will receive an injection of contrast fluid before the scan. This may result in a metallic taste in the mouth, feeling of heat, nausea, and at the injection site a burning sensation, pain, swelling, bruise, a crust or an infection. Rarely does an allergic reaction to the contrast fluid occur with hot flashes, sweats, rashes, breathing problems and nausea. A serious allergic reaction can be life threatening.
* X-rays: Patient will be exposed to radiation, about the same as we are exposed to in daily life in 1 to 2 weeks. Radiation can cause damage to genetic material.
* Bone scan: Patient will be exposed to radiation, about the same as to which we are exposed in daily life in 1 to 2 years. Radiation can cause damage to the body's genetic material.

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

* Stage IIIB/IIIC (not amenable to surgery, radiation or multi modality therapy) or IV NSCLC at the time of study entry.
* Histologically or cytologically confirmed diagnosis of NSCLC that is EGFR wt (for EGFR mutations that predict sensitivity to EGFR therapy, including, but not limited to exon 19 deletions and exon 21 L858R substitution mutations), ALK rearrangement negative as assessed by a validated test as part of the participant*s standard of care and has MET*ex14 mutation determined by Novartis-designated central laboratory or by a locally performed, tissue-based test, validated according to local regulation.
* At least one measurable lesion as defined by RECIST 1.1.
* Participants must have progressed on one or two prior lines of systemic therapy for advanced/metastatic disease (stage IIIB/IIIC [not candidates for surgery, radiation or multi modality therapy] or IV NSCLC) and must be docetaxel naive and be candidates for single agent chemotherapy (docetaxel). Participants must have progressed on or after the last therapy before study entry.
* ECOG performance status of 0 or 1.

Exclusion criteria

* Prior treatment with any MET inhibitor or HGF-targeting therapy
* Participants with known druggable molecular alterations (such as ROS1 and RET rearrangements, BRAF mutation, KRAS mutation, NTRK fusions, etc.) which might

be a candidate for alternative targeted therapies.
* Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
* Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome.
* Clinically significant, uncontrolled heart diseases

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:	Recruitment stopped
Start date (anticipated):	28-06-2021
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Docetaxel
Generic name:	Taxotere
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tabrecta
Generic name:	Capmatinib

Ethics review

Approved WMO Date:	21-07-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-11-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-03-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-04-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-05-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-04-2022

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2020-001578-31-NL
CCMO	NL74228.091.20