A multicentre single-arm phase II trial of amivantamab, lazertinib plus bevacizumab in patients with EGFR-mutant advanced NSCLC with progression on previous third generation EGFR TKI

Published: 06-03-2023
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-512288-29-00 check the CTIS register for the current data. The aim of this prospective single-arm phase II study is to evaluate the efficacy of amivantamab and bevacizumab added to continued...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory and mediastinal neoplasms benign (excl mesotheliomas)
Study type	Interventional

Summary

ID

NL-OMON56289

Source
ToetsingOnline

Brief title
ETOP 18-21 AMAZE-lung

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: ETOP IBCSG Partners,Janssen Pharmaceutica

Intervention

Keyword: Amivantamab, EGFR-mutant (exon 19 deletion and/or L858R), Lazertinib, NSCLC

Outcome measures

Primary outcome

Objective response rate (ORR) at 12 weeks according to RECIST v1.1

Secondary outcome

- Duration of Response (DoR)

-Progression-free survival (PFS) according to RECIST v1.1

- Disease control rate (DCR) according to RECIST v1.1

- Overall survival (OS)

- Safety and tolerability (CTCAE v5.0)

Study description

Background summary

The third-generation EGFR-TKIs osimertinib is currently the preferred first-line treatments for patients with metastatic, EGFR-mutant NSCLC. Osimertinib or lazertinib (for Korea) are also indicated upon disease progression after first-line therapy with a first- or second-generation EGFR-TKI when the T790M resistance mutation is documented. The standard treatment following progression on osimertinib or lazertinib is platinum and pemetrexed.
Mechanisms of acquired resistance to third-generation EGFR-TKIs in the first-line setting include C797S mutation (7%) and MET amplification (7-66%).

MET amplification is a mechanism of acquired resistance following treatment with a third-generation EGFR-TKI in the first- or second-line setting. Amivantamab (JNJ-61186372), is an anti-EGFR-MET bispecific antibody that targets activating and resistance mutations of EGFR, as well as the MET pathway. Amivantamab monotherapy, has shown a response rate of 19% in chemo-naïve patients post osimertinib treatment.
Lazertinib is an oral, third-generation, EGFR-TKI being developed for the treatment of NSCLC. It is a brain-penetrant, irreversible EGFR-TKI that targets the T790M mutation and activating EGFR-mutations exon 19 deletion and L858R, while sparing wild type-EGFR. Lazertinib is approved in Korea for the treatment of patients with EGFR T790M-mutant advanced NSCLC who have previously received EGFR-TKI therapy.
The combination of amivantamab plus lazertinib after osimertinib appears to have higher activity and response durability compared to the Amivantamab monotherapy, with potentially improved CNS protection.
Increased VEGF is associated with resistance to EGFR inhibition and resistance to EGFRTKI may be associated with increased tumour and stromal VEGF levels. Furthermore, dual inhibition of both the VEGFR and the EGFR pathway can abrogate resistance to EGFR-TKIs and anti-angiogenic agents may increase intra-tumour uptake of anti-cancer drugs by altering tumour vessel physiology.

Study objective

This study has been transitioned to CTIS with ID 2024-512288-29-00 check the CTIS register for the current data.

The aim of this prospective single-arm phase II study is to evaluate the efficacy of amivantamab and bevacizumab added to continued treatment with a third-generation EGFRTKI (osimertinib or lazertinib), for patients with EGFR-mutant advanced NSCLC, progressing on prior treatment on osimertinib or lazertinib.

Study design

Single-arm phase II trial, aiming to evaluate the efficacy of amivantamab, lazertinib and bevacizumab in patients with EGFRmutant advanced NSCLC and progression on previous treatment with a third-generation EGFR-TKI, based on the primary endpoint of ORR.

Intervention

The patients will be given three different drugs called amivantamab, lazertinib and bevacizumab until disease progression or unacceptable toxicity. Amivantamab and bevacizumab are given by infusion once every 3 weeks.
The Amivantamab dose given varies according to each patient*s body weight. It is 1750 mg for patients below 80 kg (in cycle1: 350 mg on day 1, 1050 mg on day

2, 1400 mg on day 8, 1400 mg on day 15, In cycle 2: 1400 mg on day 1, From cycle 3 on: 1750 mg on day 1).
A bevacizumab dose of 15 mg per kilogram body weight will be given once every 3 weeks by infusion.
Lazertinib is an oral drug which is given in 3x 80 mg tablets to be taken once a day.
Furthermore, the following study procedures/assessments will be performed: Physical examination (including body weight, temperature, pulse rate and blood pressure measurements), questions about general wellbeing to assess performance or activity level, blood and urine tests, Radiological scans by CT and MRI of the brain, cardiac function tests (ECG and LVEF), lung cancer biopsy.

Study burden and risks

The study procedures and tests can be found in the protocol (pages 18-21)
- Drawing blood can cause pain, redness, swelling or bruising at or near where the needle enters the vein and can increase the risk of infection.
- There might be a risk of an allergic reaction related to contrast dye during radiological test.
- Possible serious side effects for amivantamab:
Infusion-related side effects may occur during or shortly after an amivantamab infusion is given. The most common side effects are nausea, chills, shortness of breath, flushing, chest discomfort and vomiting. Less common infusion-related side effects include fever, cough, itching, rash, changes in blood pressure, fast heart rate and breathing rate, dizziness and decreased oxygen level in the blood.
Very common (may affect more than 1 in 10 people) side effects are:
Rash, Infection or inflammation of the skin around the fingernail and other nail problems, Itching, Dry or cracked skin, Infusion-related reactions, Inflammation of the mouth or mouth sores, Constipation, Nausea, Vomiting, Diarrhoea, Low levels of a blood protein called albumin (can cause generalized swelling), Decreased appetite, Decreased blood calcium level that usually does not cause symptoms but when severe, can cause muscle twitching and/or contractions, abnormal heart beats or seizures, Decreased levels of potassium in the blood that usually does not cause symptoms but when severe, can cause abnormal heart rates that could be serious and life threatening, Tiredness, Swelling in the hands, feet or limbs, Increased levels of liver enzymes in the blood that usually does not cause symptoms, but can indicate liver damage, Dizziness, Muscle aches or pain.
Common (may affect up to 1 in 10 people) side effects are:
Eye problems (such as dry eye, itchy eyes, vision problems, abnormal growth of eyelashes), Abdominal pain, Inflammation of the lung (can cause sudden difficulty in breathing, cough or fever), Low levels of magnesium in the blood (can cause weakness and muscle cramping).
- Possible serious side effects for amivantamab and lazertinib combination therapy:
Rashes, Toxic epidermal necrolysis, Venous thromboembolism, Lung Inflammation.

Very common (may affect more than 1 in 10 people) side effects are:
Rash, Infection or inflammation of the skin around the fingernail, Dry or cracked skin, Itching, Infusion-related reactions, Inflammation of the mouth or mouth sores, Nausea, Constipation, Diarrhoea.
Common (may affect up to 1 in 10 people) side effects are:
Eye problems (dry or itchy eye, vision blurred, visual impairment, growth/thickening of eyelashes, conjunctivitis that is not infective, corneal irritation, redness, pain, sensitivity to light, tearing, inflammation, floaters), Inflammation of the lung, Muscle pain, Heartburn.
- Possible side effects for bevacizumab:
The side effects listed below were seen when bevacizumab was given together with chemotherapy. This means the side effects may not have been caused by bevacizumab.
Severe side effects with bevacizumab that may be very common (may affect more than 1 in 10 people):
high blood pressure, feeling of numbness or tingling in hands or feet, decreased number of cells in the blood, including white cells that help to fight against infections (this may be accompanied by fever), and cells that help the blood to clot, feeling weak and having no energy, tiredness, diarrhoea, nausea, vomiting and abdominal pain.
Severe side effects with bevacizumab that may be common (may affect up to 1 in 10 people):
perforation of the gut, bleeding, including bleeding in the lungs in patients with non-small cell lung cancer, blocking of the arteries by a blood clot, blocking of the veins by a blood clot, blocking of the blood vessels of the lungs by a blood clot, blocking of the veins of the legs by a blood clot, heart failure, problems with wound healing after surgery, redness, peeling, tenderness, pain, or blistering on the fingers or feet, decreased number of red cells in the blood, lack of energy, stomach and intestinal disorder, muscle and joint pain, muscular weakness, dry mouth in combination with thirst and/or reduced or darkened urine, inflammation of the moist lining of mouth and gut, lungs and air passages, reproductive, and urinary tracts, sores in the mouth and the tube from the mouth to the stomach, which may be painful and cause difficulty swallowing, pain, including headache, back pain and pain in the pelvis and anal regions, localised pus collection, infection, and in particular infection in the blood or bladder, reduced blood supply to the brain or stroke, sleepiness, nose bleed, increase in heart rate (pulse), blockage in the gut or bowel, abnormal urine test (protein in the urine), shortness of breath or low levels of oxygen in the blood, infections of the skin or deeper layers under the skin, fistula: abnormal tube-like connection between internal organs and skin or other tissues that are not normally connected, including connections between vagina and the gut in patients with cervical cancer.
Severe side effects with bevacizumab of unknown frequency:
serious infections of the skin or deeper layers under the skin, especially if you had holes in the gut wall or problems with wound healing, allergic reactions (the signs may include difficulty breathing, facial redness, rash,

low blood pressure or high blood pressure, low oxygen in your blood, chest pain, or nausea/vomiting), a negative effect on a woman*s ability to have children, a brain condition with symptoms including seizures (fits), headache, confusion, and changes in vision (Posterior Reversible Encephalopathy Syndrome or PRES), symptoms that suggest changes in normal brain function (headaches, vision changes, confusion, or seizures), and high blood pressure, an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections), clogging of a very small blood vessel(s) in the kidney, abnormally high blood pressure in the blood vessels of the lungs which makes the right side of the heart work harder than normal, a hole in the cartilage wall separating the nostrils of the nose, a hole in the stomach or intestines, an open sore or hole in the lining of the stomach or small intestine (the signs may include abdominal pain, feeling bloated, black tarry stools or blood in your stools (faeces) or blood in your vomit), bleeding from the lower part of the large bowel, lesions in the gums with an exposed jaw bone that does not heal and may be associated with pain and inflammation of the surrounding tissue, hole in the gall bladder (symptoms and signs may include abdominal pain, fever, and nausea/vomiting).
Very common side effects with bevacizumab that were not severe (may affect more than 1 in 10 people):
constipation, loss of appetite, fever, problems with the eyes (including increased production of tears), changes in speech, change in the sense of taste, runny nose, dry skin, flaking and inflammation of the skin, change in skin colour, loss of body weight, nose bleeds.
Common side effects with bevacizumab that were not severe (may affect up to 1 in 10 people):
voice changes and hoarseness.
Patients older than 65 years may have an increased risk of having the following side effects with bevacizumab:
blood clot in the arteries which can lead to stroke or heart attack, reduction in the number of white blood cells and cells that help the blood to clot, diarrhoea, sickness, headache, fatigue, high blood pressure.

Contacts

Public
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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 non-squamous NSCLC, stage IIIB/C (not amenable to radical therapy) or stage IV according to 8th TNM classification.
2. Presence of the sensitising EGFR-mutation (only patients with exon 19 deletion and/or L858R are eligible) and documentation of T790M status, tested locally by an accredited laboratory.
3.Radiologically confirmed disease progression on previous treatment with osimertinib or lazertinib. Treatment with osimertinib or lazertinib must have been stopped at least 8 days before enrolment.
4.Achieved objective clinical benefit from osimertinib or lazertinib treatment (e.g., documented PR/ CR or SD for >=6 months while on osimertinib or lazertinib treatment).
5.Measurable disease as defined according to RECIST v1.1.
6. ECOG performance status 0-2
7. Adequate haematological, renal and liver function.

Exclusion criteria

1. Patients with known small cell lung carcinoma (SCLC).
2. Patients with symptomatic brain metastases. Patients with asymptomatic or previously treated and stable brain metastases may participate in this study. Patients who have received definitive radiotherapy or surgery for symptomatic or unstable brain metastases and have been clinically stable and asymptomatic for at >= 2 weeks before enrolment are eligible, provided they have been either

off corticosteroid treatment or are receiving low-dose corticosteroid treatment (<=10 mg/day prednisone or equivalent) for at least 2 weeks prior to enrolment.
3. Patients with an active or past medical history of leptomeningeal disease.
4. Patients with untreated spinal cord compression. Patients who have been definitively treated with surgery or radiotherapy and have a stable neurological status for >=2 weeks prior to enrollment
are eligible provided they are off corticosteroid treatment or are receiving low-dose corticosteroid treatment <=10 mg/day prednisone or equivalent.
5. Patients with unresolved adverse events (other than alopecia) from prior anticancer therapy that have not resolved to grade <=1 or baseline.
6. Patients with positive hepatitis B or hepatitis C antibody or other clinically active infectious liver disease .
7. Patients who are positive for HIV.
8. Patients with active cardiovascular disease.
9. Patients with interstitial lung disease (ILD), including drug-induced ILD or radiation pneumonitis.
10. Patients with a history of haemoptysis (>=2.5 mL of bright red blood per episode) within 1 month prior to enrolment.
11. Patients with evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation).
12. History of hypersensitivity to either the drug substance or any excipients in amivantamab, lazertinib and/ or bevacizumab.
13. Prior chemotherapy, prior treatment with bevacizumab or another anti-angiogenic inhibitor or prior treatment with a MET/EGFR-targeting antibody.
14. Patients with a significant genetic predisposition to venous thromboembolic events
(VTE, such as factor V Leiden) or patients with a history of VTE who are not receiving
appropriate therapeutic anticoagulation according to NCCN or local guidelines.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-08-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Leclaza
Generic name:	Lazertinib
Product type:	Medicine
Brand name:	Rybrevant
Generic name:	Amivantamab
Product type:	Medicine
Brand name:	Zirabev
Generic name:	Bevacizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-03-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	26-06-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	31-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	24-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-11-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-01-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-02-2024
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
EU-CTR	CTIS2024-512288-29-00
EudraCT	EUCTR2021-002337-42-NL
CCMO	NL83012.041.22
Other	NTC05601973