# A Phase II, two arm study to investigate tepotinib combined with osimertinib in MET amplified, advanced or metastatic non-small cell lung cancer (NSCLC) harboring activating EGFR mutations and having acquired resistance to prior osimertinib therapy (INSIGHT 2 Study)

Published: 09-07-2019
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The main objective of this study is to assess the efficacy of tepotinib combined with osimertinib inparticipants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by FISH.The secondary objectives are the following:...

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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-OMON52430

**Source**
ToetsingOnline

**Brief title**
MS200095-0031

### Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

**Synonym**
locally advanced or metastic non-small cell lung carcinoma, lung cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Merck
**Source(s) of monetary or material Support:** pharmaceutical industry

## Intervention

**Keyword:** non-small cell lung cancer, osimertinib, phase 2, tepotinib

## Outcome measures

### Primary outcome

The primary endpoint is objective response (confirmed complete response [CR] or partial response [PR]) determined according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as per Independent Review Committee (IRC).

### Secondary outcome

The secondary endpoints are:

- Objective response (complete response [CR] or partial response [PR]) determined according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as per Independent Review Committee (IRC).

- Occurrence of Adverse Events (AEs) and treatment related AEs.

- Occurrence of abnormalities (Grade >= 3) in laboratory test values (hematology and coagulation, biochemistry) and urinalysis.

- Occurrence of markedly abnormal vital sign measurements, change in body weight, and Eastern Cooperative Oncology Group (ECOG) performance status.

- Occurrence of clinically significantly abnormal electrocardiograms (ECGs).

- Objective response according to RECIST Version 1.1 assessed by Investigator.

- Confirmed CR assessed by IRC and by Investigator.

- Duration of response assessed from CR or PR until progressive disease (PD), death, or last tumor assessment assessed by IRC and by Investigator.

- Disease control (confirmed CR + PR or stable disease [SD] lasting at least 12 weeks) as assessed by IRC and by Investigator.

- Progression free survival according to RECIST Version 1.1 by IRC and by Investigator.

- Overall survival

- Patient-reported outcomes/health-related quality of life as reported using the following:

• EuroQol Five Dimension Five Level Scale

• European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30

• Non-Small Cell Lung Cancer Symptom Assessment Questionnaire.

- Single- and multiple-dose PK profile of osimertinib, tepotinib, and their metabolites including but not limited to AUC0-t, Cmax, and tmax after first dose (Day 1) and after multiple study intervention dose administrations (Day 15) (safety run-in).

- Population PK profile of osimertinib, tepotinib, and their metabolites, including, but not limited to, CL/f and VZ/f based on sparse PK sampling on Day 1, Cycle 1 and 2.

- Mutation status in EGFR and other pathways.

# Study description

**Background summary**

Lung cancer remains the leading cause of cancer death worldwide. Approximately 85% of patients have (non-small cell lung cancer) NSCLC and most present with advanced stage disease (not amenable to curative intent). Novel targeted therapies that interfere with specific molecular signaling pathways have emerged as a new standard option for selected patients with epidermal growth factor receptor (EGFR) mutation, including the oral EGFR-TKIs. EGFR-TKIs inhibit the intracellular tyrosine kinase domain of the EGFR and therefore block the signal transduction pathways implicated in the proliferation and survival of cancer cells.

Unfortunately, most patients ultimately progress on epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) treatment via a resistance mechanism most commonly related to EGFR such as the T790M mutation (Sullivan et al. 2017). This limitation has been overcome by the introduction of 3rd generation TKIs, particularly osimertinib. Currently, osimertinib is the only 3rd generation EGFR TKI approved for the treatment of T790M positive patients who have progressed on 1st or 2nd generation EGFR TKIs. Osimertinib is also approved as first-line therapy for advanced EGFR mutant (EGFRm+) NSCLC, regardless of T790M mutation status. However, despite the robust clinical activity exerted by osimertinib, patients inevitably develop secondary resistance to this treatment, which poses a significant challenge due to the paucity of post-osimertinib pharmacological options available to date (Leonetti et al. 2019).

Next to EGFR-related resistance, MET gene amplification constitutes the most frequent cause of bypass pathway activation as an acquired resistance mechanism to EGFR TKIs (Wu et al. 2017). When osimertinib was given as a first-line therapy, MET amplification was the most common resistance mechanism, encountered in 15% of patients. Tepotinib is a novel, highly selective, reversible adenosine triphosphate (ATP)-competitive, small molecule inhibitor of MET. Tepotinib has already shown signals of clinical efficacy in the previous INSIGHT study (NCT01982955) in patients with MET amplified, EGFR TKI-relapsed, T790M-negative, NSCLC in combination with the 1st generation EGFR TKI gefitinib (Wu et al. 2018).

Based on the available preclinical and clinical experience with tepotinib in combination with EGFR-TKIs, the INSIGHT 2 study (MS200095-0031) will investigate the combination of osimertinib and tepotinib in patients who relapsed on previous first-line osimertinib due to MET amplification. The study introduces a single agent tepotinib arm to additionally assess the contribution of tepotinib to the osimertinib and tepotinib combination therapy. There is

currently no personalized treatment option available for these selected NSCLC patients and therefore constitutes a clinical condition with high unmet medical need.

## Study objective

The main objective of this study is to assess the efficacy of tepotinib combined with osimertinib in
participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by FISH.

The secondary objectives are the following:
To assess the efficacy of tepotinib combined with osimertinib in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification determined centrally by blood-based next generation
sequencing.
To assess the efficacy of tepotinib monotherapy in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification determined centrally by FISH.
To assess tolerability and safety in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification treated with the combination of tepotinib plus osimertinib.
To assess tolerability and safety in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification treated with tepotinib monotherapy.
To further assess efficacy of tepotinib combined with osimertinib in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by FISH

## Study design

A Phase II two-arm, open-label study.

## Intervention

Study participation is composed of the following stages:
1. Prescreening (performed after progression on first-line osimertinib): After providing written Prescreening consent, MET amplification status will be assessed centrally by FISH or by reviewing pre-existing local FISH results using tumor tissue (TBx), and centrally by blood-based next generation sequencing (LBx).

2. Screening: After providing written consent at Screening, study eligibility will be assessed within -28 to -1 days prior to Day 1 of study intervention.

3. Treatment period:
a. For the safety run-in, an initial subset of at least 6 participants, who are detected to be MET amplified with any of the methods (central/local TBx or

central LBx) described at Prescreening, will be enrolled to confirm the combination dose of tepotinib 500 mg once daily and osimertinib 80 mg once daily; the decision will be made by the Safety Monitoring Committee (SMC) based on predefined dose-limiting toxicity criteria and supported by a Bayesian Optimal Interval Design (BOIN).

b. For the main treatment, eligible participants who are detected to be MET amplification positive by central or local FISH (TBx) will be randomly assigned in a ratio of 2:1 to either the combination of tepotinib at a dose defined by the SMC and osimertinib at the recommended daily dose of 80 mg or tepotinib alone at the daily dose of 500 mg (as currently used in the Phase II single agent VISION study) in cycles of 21-day duration until disease progression (according to RECIST Version 1.1), death, adverse event (AE) leading to discontinuation, study withdrawal or consent withdrawal.

4. Treatment follow-ups (for all participants): End of Treatment (EoT) Visit will be conducted within 14 days after last dose of study intervention.
5. Safety follow-up Visit (for all participants): 30 ± 3 days after the last dose of study intervention for those who discontinue study intervention permanently.
Participants who discontinue study intervention for reasons other than (progressive disease) PD or death will have additional visits for tumor assessments every 6 weeks until 9 months after first administration of study intervention and every 12 weeks thereafter until disease progression. Survival follow-up is to be performed every 3 months (± 2 weeks) at clinic visits or by telephone contact.

**Study burden and risks**

In a pharmaceutical trial like this one, every risk or side effect cannot be predicted. Each person*s reaction to a test drug may be different. Based on data available from participants having received 500 mg tepotinib monotherapy once daily, the most frequently observed adverse events (in >=15% of participants) irrespective of severity and relationship to tepotinib were: blood creatinine increased; constipation (blockage of stool); decreased appetite'; diarrhea (loose stool); edema peripheral (swelling caused by excess fluid); fatigue (feeling tired); hypoalbuminemia (low level of albumin in the blood, which can cause swelling, muscle weakness, and cramps); nausea (feeling sick); dyspnea (labored breathing). Liver failure that rarely leads to death may occur in participants with hepatocellular cancer and extensive liver involvement from metastases in other disease settings (including NSCLC).

Very common side effects of osimertinib (observed in 10% or more of people taking osimertinib) include diarrhea (loose stool); nausea; rash; dry skin; pruritus (itching skin); problems with the eyes; nail toxicity (changes in the nails, including redness, tenderness, pain, inflammation, brittleness,

separation from nailbed, and shedding); stomatitis (mouth ulcers); constipation; fatigue (feeling tired); decreased appetite; cough; back pain; headache; lack of healthy red blood cells that carry oxygen (anemia); decreased numbers of several types of white blood cells; decreased numbers of platelets in your blood; high levels of magnesium in the blood; low blood levels of sodium in the blood.
Osimertinib may cause uncommon but serious side effects, including lung problems, heart problems, and eye problems. In clinical research studies, 3.9% of participants experienced interstitial lung disease (ILD), a disorder which may cause scarring of the lung, and 2.6% of participants experienced cardiomyopathy, a type of heart disease. These lung and heart problems may, in the worst case, lead to death. In addition, some participants experienced keratitis, an inflammation of the surface of the eye, which may cause impaired eyesight, redness, pain, and light sensitivity. Osimertinib is also known to cause harm to an unborn baby.

## 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

Participants are eligible to be included in the study only if all the following criteria apply:
1. Are >= 18 years of age (or having reached the age of majority according to local laws and regulations, if the age of majority is > 18 years of age [ie, >= 20 years of age in Japan]), at the time of signing the informed consent.
2. Are participants with the following:
a) Locally advanced or metastatic NSCLC histology (confirmed by either histology or cytology) with documented activating EGFR mutation
b) Presence of at least 1 independently verified measurable lesion in accordance with RECIST 1.1, that can be accurately assessed at baseline with >= 10 mm in the longest diameter (except lymph nodes which must have short axis >= 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI), which is suitable for accurate repeated measurements and that preferably was not previously irradiated or biopsied
c) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and a minimum life expectancy of 12 weeks
d) Acquired resistance on previous first-line-osimertinib. Participants must meet both of the following 2 criteria:
-Radiological documentation of disease progression first-lineosimertinib.
-Objective clinical benefit documented during previous osimertinib therapy, defined by either partial or complete radiological response, or durable stable disease (SD) (SD should last > 6 months) after initiation of osimertinib
e) Have received only first line osimertinib as a prior line of therapy in the noncurative advanced or metastatic NSCLC setting
f) MET amplification as determined by either FISH testing (central or local) on tumor tissue (TBx) or central blood-based next generation sequencing (LBx). Tumor and blood samples must be collected following progression on prior first-line osimertinib at Prescreening.
-Submission of tumor tissue and blood sample obtained after progression on first line osimertinib, is mandatory for all patients for MET amplification testing.
-Submission of tumor tissue during Prescreening or Screening is mandatory for patients with tumor tissue tested by local FISH, to confirm MET amplification status. Central testing is not mandated prior to the start of study treatment
3. Woman: no woman of childbearing potential (WOCBP) or, use a highly effective contraception. Man: contraception or no intercourse with a WOBCP.

## Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:
1. Spinal cord compression or brain metastasis unless asymptomatic, stable or not requiring steroids for at least 2 weeks prior to start of study intervention. Prior radiotherapy or surgery for brain metastases such as stereotactic radiosurgery/gamma knife must have been completed >= 2 weeks, all others >= 4 weeks prior to start of therapy. Participants with leptomeningeal disease are ineligible.
2. Any unresolved toxicity Grade 2 or more according to National Cancer Institute-Common Terminology Criteria for Adverse Events Version (NCI-CTCAE) version 5, from previous anticancer therapy with the exception of alopecia.
3. Need for transfusion within 14 days prior to the first dose of study intervention.
4. Participants who have brain metastasis as the only measurable lesion
5. Inadequate hematological function:
- Hemoglobin < 8.5 g/dL
- Neutrophils < 1.5 × 109/L
- Platelets < 100 × 109/L.
6. Inadequate liver function:
- Total bilirubin > 1.5 × ULN
- AST/ALT/ALP > 3 × ULN
- For participants with liver metastases:
i. Total bilirubin > 1.5 × ULN
ii. AST/ALT/ALP > 5 × ULN
iii. For participants with bone metastases: ALP > 5 × ULN.
7. Inadequate renal function:
- Renal impairment as evidenced by serum creatinine >= 1.5 × ULN, or creatinine clearance (CrCl) < 30 mL/min calculated by the Cockcroft- Gault formula (24-hour CrCl might be requested by the Investigator for confirmation, if calculated CrCl is < 50 mL/min. In such case, participants with 24-hour CrCl < 30 mL/min should be excluded). CrCl (mL/min) = [(140 - age(year)) × weight(kg)] 72 × serum creatinine (mg/dL) {× 0.85 for females}
8. History of ILD or interstitial pneumonitis including radiation pneumonitis that required steroid treatment.
9. Impaired cardiac function:
-Left ventricular ejection fraction < 45% defined by echocardiography
- Grade 4 arrhythmia (NCI-CTCAE v5.0)
-Serious arrhythmia
-Unstable angina pectoris
-Congestive Heart Failure New York Heart Association III and IV
- Myocardial infarction, stroke, or transient ischemic attack within the last 6 months prior to study entry.
10. Corrected QT interval by Fredericia (QTcF) > 470 ms for women and > 450 ms for men at screening.Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as hypokalemia, 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 Torsade de Pointes.
11. Hypertension uncontrolled by standard therapies (not stabilized to < 150/90 mmHg).
12. Contraindication to the administration of osimertinib.
13. Medical history of liver fibrosis/cirrhosis.
14. Past or current history of neoplasm other than NSCLC, except for curatively treated non-melanoma skin cancer, in situ carcinoma of the cervix, benign prostate neoplasm/hypertropia,or other cancer curatively treated and with no evidence of disease for at least 5 years.
15. Medical history of difficulty swallowing, malabsorption, or other chronic gastrointestinal disease, or conditions that may hamper compliance and/or absorption of the tested product.
16. Major surgery within 28 days prior to Day 1 of study intervention.
17. Known human immunodeficiency virus positivity.
18. Known hypersensitivity to any of the study intervention ingredients.
19. Has not received an EGFR-TKI containing treatment directly prior to enrollment into the study, ie, chemotherapy or checkpoint inhibitor treatment with/without vascular endothelial growth factor inhibitors either in monotherapy or in combination are allowed, if these treatments do not represent the most recent treatment lines prior to enrollment
20. Prior treatment with other agents targeting the Hepatocyte Growth Factor (HGF)/MET pathway such as crizotinib, capmatinib, savolitinib, foretinib, glesatinib, cabozantinib, merestinib, onartuzumab, rilotumumab, emibetuzumab, and ficlatuzumab.
21. Participants currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of study intervention) medications or herbal supplements known to be potent inducers of CYP3A4.
22. Participation in another interventional clinical study (except those participants who were solely involved in other studies where the investigational product was osimertinib in the first-line of therapy) within the 30 days prior to randomization/first dose.

# Study design

## Design

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| 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): | 23-01-2020 |
| Enrollment: | 3 |
| Type: | Actual |

### Medical products/devices used

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

## Ethics review

Approved WMO

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|---|---|
| Date: | 09-07-2019 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

Approved WMO

| | |
|---|---|
| Date: | 07-10-2019 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

Approved WMO

| | |
|---|---|
| Date: | 19-12-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

Approved WMO

| | |
|---|---|
| Date: | 09-06-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 02-07-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 07-09-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 06-03-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 08-03-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 06-08-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 18-02-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 18-03-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek |

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|---|---|
| | (Assen) |
| Approved WMO Date: | 22-07-2022 |
| 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 |
|---|---|
| EudraCT | EUCTR2019-001538-33-NL |
| ClinicalTrials.gov | NCT03940703 |
| CCMO | NL70294.056.19 |