A Phase 1b Dose Escalation and Dose Expansion Study Evaluating the Safety, Pharmacokinetics, and Antitumor Activity of Furmonertinib in Patients with Advanced or Metastatic Non-Small Cell Lung Cancer with Activating EGFR or HER2 Mutations

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This study has been transitioned to CTIS with ID 2023-508349-42-00 check the CTIS register for the current data. Stage 1 Primary ObjectiveTo evaluate the safety and tolerability, determine the expansion dose, and characterize dose-limiting...

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

Summary

ID

NL-OMON53437

Source
ToetsingOnline

Brief title
A study of Furmonertinib in Patients with NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Patients with Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) with mutations in

a gene called epidermal growth factor receptor (EGFR)/Lung Cancer

Research involving
Human

Sponsors and support

Primary sponsor: ArriVent BioPharma, Inc.
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Furmonertinib, NSCLC, open-label, Phase 1b

Outcome measures

Primary outcome

Stage 1 Primary Endpoint

• Incidence and severity of adverse events (AEs), including DLTs, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)

Stage 2 Primary Endpoints

• Stage 2, Cohorts 1, 2, and 3 only: Confirmed ORR, defined as the percentage of patients with a confirmed CR or PR relative to the total number of patients. Confirmation of the response is based on a subsequent assessment, at least 28 days later, as determined by investigator assessment using RECIST v1.1

• Stage 2, Cohort 4 only: Confirmed ORR as determined by BICR assessment using RECIST v1.1

Secondary outcome

Stage 1 Secondary Endpoints

• Confirmed objective response rate (ORR), defined as the percentage of patients with a confirmed complete response (CR) or partial response (PR)

relative to the total number of patients. Confirmation of response is based on a subsequent assessment, at least 28 days later, as determined by investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1)

• Duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and depth of response (DpR) evaluated by investigator assessment per RECIST v1.1

• Overall survival (OS)

• Central nervous system (CNS)-confirmed ORR (CNS ORR) and DOR (CNS DOR) via modified RECIST evaluated by blinded independent central review (BICR) in patients with CNS lesion(s) on brain imaging performed at screening

• Plasma concentrations of furmonertinib and its major metabolite (AST5902) at specified time points

Stage 1, Cohort 1 Backfill only:

• Plasma concentrations of furmonertinib and its major metabolite (AST5902) at specified time points

• Plasma concentrations of midazolam and its metabolite (1-OH-midazolam) at specified time points

Stage 2 Secondary Endpoints

Stage 2, Cohorts 1, 2, and 3 only:

• DOR, DCR, PFS, and DpR evaluated by investigator assessment per RECIST v1.1

• OS

• CNS ORR and CNS DOR via modified RECIST evaluated by BICR in patients with CNS lesion(s) on brain imaging performed at screening

Stage 2, Cohort 4 only:

• Confirmed ORR, as well as DOR, DCR, PFS, and DpR evaluated by investigator assessment per RECIST v1.1

• DOR, DCR, PFS, and DpR as determined by BICR assessment using RECIST v1.1

• OS

• CNS ORR and CNS DOR via modified RECIST evaluated by BICR in patients with CNS lesion(s) on brain imaging performed at screening

Stage 2, all cohorts:

• Incidence and severity of AEs, with severity determined according to NCI CTCAE v5.0

Stage 2, all cohorts:

• Plasma concentrations of furmonertinib and its major metabolite (AST5902) at specified time points

Stages 1 and 2 Exploratory Endpoints

Stage 1 and Stage 2, Cohorts 1, 2, and 3 only:

• Confirmed ORR, as well as DOR, DCR, PFS and DpR as determined by BICR assessment using RECIST v1.1

Stages 1 and 2, all cohorts:

• Response rate and DOR per Response Assessment in Neuro-Oncology (RANO)-leptomeningeal metastases (LM) criteria by BICR

Stages 1 and 2, all cohorts:

• Change from baseline in patient-reported symptoms and their impact on functioning and health-related quality of life, and the overall burden of side effects, as measured by the European Organization for Research and Treatment of

Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30), EORTC QLQ Lung Cancer Module Core 13 (EORTC QLQ-LC13), and NSCLC Symptom Assessment Questionnaire (NSCLC SAQ)

Stages 1 and 2, all cohorts:

• Correlation of furmonertinib and AST5902 PK with primary, secondary, and exploratory endpoints in patients treated with furmonertinib

Stages 1 and 2, all cohorts:

• Change in tumor tissue gene mutation profile at baseline, during treatment, and at disease progression

• Consistency and change of circulating tumor DNA (ctDNA) gene mutation profile in the peripheral blood at baseline, during treatment, and disease progression samples

• EGFR mutation status in ctDNA in peripheral blood or possible changes in resistant genes at baseline, during treatment, and at disease progression

• Correlation of exploratory biomarkers with primary, secondary, and exploratory endpoints in patients treated with furmonertinib

Study description

Background summary

In laboratory studies the study drug has been shown to shrink or slow the growth of several different types of cancers or tumors in animals whose tumor cells have a change in the EGFR or HER2 gene. This change in the EGFR or HER2 gene can cause cells to grow abnormally and develop into cancer. It is hoped that the study drug will stop tumor cells with the abnormal EGFR or HER2 genes from growing rapidly.

The study drug is experimental, which means that health authorities have not

approved the study drug for the treatment of this type of NSCLC. Doctors are not allowed to prescribe or use this study drug outside research.

Study objective

This study has been transitioned to CTIS with ID 2023-508349-42-00 check the CTIS register for the current data.

Stage 1 Primary Objective
To evaluate the safety and tolerability, determine the expansion dose, and characterize dose-limiting toxicities (DLTs) of escalating doses of furmonertinib administered daily to patients with locally advanced or metastatic NSCLC with activating EGFR or HER2 mutations
Stage 1 Secondary Objectives
To make a preliminary assessment of the antitumor activity of furmonertinib in patients with locally advanced or metastatic NSCLC with activating EGFR or HER2 mutations
To characterize the pharmacokinetic (PK) properties of furmonertinib and its major metabolite (AST5902) in patients with locally advanced or metastatic NSCLC with activating EGFR or HER2 mutations
Stage 1, Cohort 1 Backfill only: To assess whether furmonertinib induces cytochrome P450 3A4 (CYP3A4) at clinically relevant exposures in patients based on drug-drug interaction (DDI) with midazolam in locally advanced or metastatic NSCLC with EGFR or HER2 mutations
Stage 2 Primary Objectives
Stage 2, Cohorts 1, 2, and 3 only: To make a preliminary assessment of the antitumor activity of furmonertinib in patients with locally advanced or metastatic NSCLC with EGFR or HER2 mutations
Stage 2, Cohort 4 only: To make a preliminary assessment of the antitumor activity of furmonertinib in patients with locally advanced or metastatic NSCLC with P-loop αC-helix compressing (PACC) mutations by BICR
Stage 2 Secondary Objectives
Stage 2, Cohorts 1, 2, and 3 only: To make a preliminary assessment of the antitumor activity of furmonertinib in patients with locally advanced or metastatic NSCLC with EGFR or HER2 mutations
Stage 2, Cohort 4 only: To make a preliminary assessment of the antitumor activity of furmonertinib in patients with locally advanced or metastatic NSCLC with PACC mutations
Stage 2, all cohorts: To evaluate the safety and tolerability of furmonertinib administered daily at the expansion dose(s) in patients with locally advanced or metastatic NSCLC with EGFR or HER2 mutations
Stage 2, all cohorts: To characterize the PK properties of furmonertinib and its major metabolite (AST5902) in patients with locally advanced or metastatic NSCLC with EGFR or HER2 mutations
Stages 1 and 2 Exploratory Objectives
Stage 1 and Stage 2, Cohorts 1, 2, and 3 only: To assess the antitumor activity of furmonertinib in patients with locally advanced or metastatic NSCLC with

activating EGFR or HER2 mutations by BICR
Stages 1 and 2, all cohorts: To assess the antitumor activity of furmonertinib in locally advanced or metastatic NSCLC patients with leptomeningeal disease (LMD) harboring activating EGFR or HER2 mutations
Stages 1 and 2, all cohorts: To assess the impact of furmonertinib on patients* disease-related symptoms and health-related quality of life
Stages 1 and 2, all cohorts: To explore the relationship between PK and endpoints which may include, but are not limited to, efficacy, safety, and patient-reported outcomes (PROs), as appropriate
Stages 1 and 2, all cohorts: To identify and/or evaluate biomarkers that are predictive of response to furmonertinib (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to furmonertinib, are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation (i.e., safety biomarkers), can provide evidence of furmonertinib activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety.

Study design

This is a Phase 1b, open-label, multicenter, dose-escalation and dose*expansion study designed to evaluate the safety, PK, and preliminary antitumor activity of furmonertinib in patients with advanced or metastatic NSCLC. Patients will be enrolled into 2 stages: Stage 1 (Dose Escalation) and Stage 2 (Dose Expansion).
Stage 1 Dose Escalation and Backfill Cohorts
Approximately 6 to 12 patients will be enrolled in the dose-escalation portion of Stage 1 and approximately 21 and up to 38 patients may be enrolled in backfill cohorts. Stage 1 will enroll locally advanced or metastatic NSCLC patients with EGFR exon 20 insertion mutations, HER2 exon 20 insertion mutations, or EGFR activating mutations (including EGFR PACC mutations and exon 19 and exon 21 mutations, such as exon 19 deletions, L858R, and L861Q, with or without EGFR T790M mutation).
Dose Level 1 (Cohort 1): 240 mg once daily (QD)
• Stage 1, Cohort 1: 3+3 Dose Escalation (n = 3 to 6)
• Stage 1, Cohort 1 Backfill (n = 15 to 28)
Note: Approximately 12 patients in Stage 1, Cohort 1 Backfill will participate in the DDI evaluation.
Dose Level 2 (Cohort 2): 320 mg QD
• There is no plan to open the 320-mg QD dose level. The maximum dose to be evaluated in this study will be 240 mg QD
Dose Level *1 (Cohort 3): 160 mg QD
• Stage 1, Cohort 3: 3+3 Dose Escalation (if needed; n = 3 to 6)
• Stage 1, Cohort 3 Backfill (n = 6 to 10)
Stage 1 Dose Escalation
The dose-escalation portion of Stage 1 will assess safety and tolerability, as

well as determine the expansion dose of furmonertinib. Dose escalation will begin with Stage 1, Cohort 1, in which furmonertinib will be administered at 240 mg by mouth (PO) QD for 21-day cycles, where the first 3 patients may be enrolled simultaneously. The maximum dose to be evaluated in this study will be 240 mg PO QD. Patients will be evaluated for DLTs to determine the expansion dose for furmonertinib in Stage 2. Patients will be closely monitored for AEs during a DLT assessment window, defined as Days 1 21 of Cycle 1. See the protocol for DLT definition and dose-escalation rules.
Patients exhibiting acceptable safety and evidence of clinical benefit (as determined by the investigator) may continue to receive furmonertinib until intolerable toxicity, loss of clinical benefit, or radiographic objective disease progression per RECIST v1.1. If the 240-mg dose is deemed to be intolerable, the furmonertinib dose may be de-escalated to 160 mg QD (Stage 1, Cohort 3), and at least 3 patients will be tested at this dose level for DLTs.
Stage 1 Backfill Cohorts
To acquire additional PK, pharmacodynamic, and safety data, patients will be enrolled in backfill cohorts. After clearance of dose escalation at 240 mg QD (Stage 1, Cohort 1), enrollment may start with Stage 1, Cohort 3 Backfill at the 160-mg dose level and patients may also be enrolled in Stage 1, Cohort 1 Backfill (240 mg QD). Patients enrolled in backfill cohorts will not be included as part of the DLT-evaluable population.
Stage 1, Cohort 1 Backfill for Evaluation of Drug-Drug Interaction with Midazolam
The DDI evaluation will be conducted at the determined expansion dose (i.e., 240 mg QD). Patients in Stage 1, Cohort 1 Backfill (240 mg QD) will be evaluated for DDI with midazolam (a sensitive CYP3A4 substrate) to determine whether furmonertinib is an inducer of CYP3A4 at a clinically relevant dose.
A cohort review committee (CRC) will be established with a remit to protect patient safety while receiving furmonertinib.
Stage 2 Dose Expansion Cohorts
Stage 2 (Dose Expansion) will consist of approximately 100 to 120 patients and will comprise 4 cohorts:
• Stage 2, Cohort 1 at 240 mg (n = 20): Previously treated, locally advanced or metastatic NSCLC patients with EGFR exon 20 insertion mutations
Note: a minimum of 10 patients previously treated with amivantamab will be enrolled.
• Stage 2, Cohort 2 at 240 mg QD (n = 20): Previously treated, locally advanced or metastatic NSCLC patients with HER2 exon 20 insertion mutations
Note: a minimum of 10 HER2-tyrosine kinase inhibitor (TKI)-naïve patients will be enrolled.
• Stage 2, Cohort 3 at 240 mg (n = 20): Previously treated, locally advanced or metastatic NSCLC patients with EGFR activating mutations (excluding EGFR exon 20 insertion mutations and PACC mutations)
• Stage 2, Cohort 4 (n = 40-60): Untreated or previously treated EGFR TKI-naïve, locally advanced or metastatic NSCLC patients with EGFR PACC mutations randomized into 2 arms comparing 160 mg QD (Arm A [n = 20]) and 240 mg QD (Arm B [n = 20]) dosing regimens; 10 additional patients per arm may be enrolled

Stage 2 will aim to obtain additional safety, tolerability, and PK data, as well as preliminary evidence of antitumor activity. Based upon the existing preliminary safety and efficacy data, and pending clearance of dose escalation at the 240-mg dose level during Stage 1, the targeted expansion dose is 240 mg for Stage 2 Cohorts 1, 2, and 3, and 160 mg and 240 mg for Stage 2, Cohort 4.

Intervention

The investigational medicinal product (IMP) for this study is furmonertinib. Furmonertinib will be administered as a single agent, PO QD in 21-day treatment cycles.

Study burden and risks

This study has three parts:
1. Screening (to see if you are eligible for the study)
2. Treatment
3. Follow-up (to check on you after treatment is finished)
Screening:
During this period, patients will have tests and assessments to see if you qualify for the study. These tests and procedures may be done over 4 weeks;
Treatment:
If patients can take part in the study, they will take a dose consisting of 4 pills daily (160 mg), or 6 pills daily (240 mg). they will take this each day, at approximately the same time, on an empty stomach, as directed by the investigator. They will take the study drug in treatment cycles of 21 days (one cycle = 21 days/3 weeks)
During this study, patients will have frequent visits to the study site during the first cycle (Cycle 1) to closely evaluate how they are doing on the study treatment. After Cycle 1 (for example, the visits will be less frequent, approximately every 3 weeks. Visits may last 2 to 9 hours.
Please refer to the procedure table In the ICF and Schedule of Assessment of the protocol for more information.
In addition, questions are asked about the medical history, demographics and eligibilty questions
Subjects will also be tested for HIV and hepatitis. Female patients will be tested for pregnancy .
The total time in the study will depend on how cancer responds to treatment. This could range from 1 day to up to 48 months.
Possible side effects that are already known are described in the Investigator's Brochure and the patient informed consent form.

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

Patients must meet the following criteria for study entry:
General Inclusion Criteria
1. Signed Informed Consent Form
2. Age >= 18 years at time of signing Informed Consent Form
3. Ability to comply with the study protocol, in the investigator*s judgment
4. Measurable disease per RECIST v1.1
Note: Measurable target lesions (TLs) can neither be subject to local therapy such as radiotherapy nor used for biopsy in the screening period; if there is only one measurable TL, this TL will be permitted to be biopsied. However, the baseline radiologic examination should be performed for this lesion at least 14 days after biopsy.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
6. Life expectancy of >= 12 weeks
7. Adequate hematologic and organ function within 14 days prior to initiation of study treatment, defined by the following:

• Absolute neutrophil count >= 1500/µL
• Hemoglobin >= 9 g/dL
• Platelet count >= 100,000/µL
• Total bilirubin <= 1.5 × upper limit of normal (ULN) or <= 3 × ULN in the presence of documented Gilbert*s Syndrome
• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 2.5 × ULN with the following exception:
- Patients with documented liver metastases may have AST and/or ALT <= 5.0 × ULN
• Creatinine clearance >= 30 mL/min based on the Cockcroft-Gault estimation:
(140 * age) × (weight in kg) × (0.85 if female)
72 × (serum creatinine in mg/dL)
• International normalized ratio (INR) <= 1.5 × ULN and activated partial thromboplastin time (aPTT) <= 1.5 × ULN
Note: This applies only to patients who are not receiving therapeutic anticoagulation. Patients receiving therapeutic anticoagulation should be on a stable dose for at least 1 week prior to Cycle 1, Day 1.
8. For women of childbearing potential (WOCBPs): Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:
• A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state >= 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
• WOCBPs must remain abstinent or use a barrier method such as a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and at least 60 days after the final dose of furmonertinib. WOCBPs must refrain from donating eggs during the treatment period and 6 months after the final dose of furmonertinib.
• Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal oral contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
Note: The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
9. For men who are not surgically sterile: Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating sperm, as defined below:
• With a female partner of childbearing potential who is not pregnant, men must remain abstinent or use a condom plus an additional contraceptive method that

together result in a failure rate of < 1% per year during the treatment period and for at least 60 days after the final dose of furmonertinib.
• Must refrain from donating sperm during the treatment period and for at least 60 days after the final dose of furmonertinib.
• With pregnant female partners, men must remain abstinent or use a condom to avoid exposing the embryo during the treatment period and for at least 60 days after the final dose of furmonertinib.
Note: The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
10. For Stage 1 dose escalation and backfill cohorts and Stage 2 Cohorts 1, 2, and 4: Patients with CNS metastases (including leptomeningeal disease) are eligible, provided they meet the following criteria:
• Measurable disease outside the CNS
• No requirement for immediate local therapy or ongoing requirement for corticosteroids as therapy for CNS metastases, with corticosteroids discontinued for >= 2 weeks prior to enrollment
• No ongoing symptoms attributed to CNS metastases
• No CNS metastases or spinal cord compression requiring anticonvulsants or corticosteroids for symptomatic control
• For patients with previously treated brain metastases
- No evidence of interim CNS disease progression between the completion of CNS directed therapy and the screening radiographic study
- Patients treated with CNS local therapy for newly identified lesions found on contrast brain magnetic resonance imaging (MRI) performed during screening may be eligible to enroll if all of the following criteria are met:
o Time since whole-brain radiation therapy (WBRT) is >= 21 days prior to first dose of study treatment, time since stereotactic radiosurgery (SRS) is >= 7 days prior to first dose of study treatment, or time since surgical resection is >= 28 days
o Do not require immediate local therapy
o Patients who undergo local treatment for lesions identified by screening contrast brain MRI may still be eligible for the study based on criteria described above.
11. Histologically or cytologically documented, locally advanced or metastatic NSCLC not amenable to curative surgery or radiotherapy
12. Consent to provide archival tumor tissue specimen (formalin-fixed, paraffin-embedded [FFPE] tissue block [preferred] or at least 15 unstained serially cut sections on slides from FFPE tumor specimen). The specimens must be provided during the screening or no later than within 30 days of Cycle 1, Day 1 and must be accompanied by a pathology report.
• It is preferred that the specimen be prepared from the most recently collected and available tumor tissue, and, whenever possible, from a metastatic

site of disease. See the laboratory manual for instructions.
13. For patients with EGFR mutations sensitive to osimertinib, the patient must have received osimertinib prior to study enrollment in regions where osimertinib is approved, including the United States (US).
14. No known acquired resistance to osimertinib (e.g., C797S or cMet amp). Other alterations should be discussed with the Medical Monitor.
Stage 1 Dose Escalation and Backfill Cohorts and Stage 2, Cohorts 1, 2, and 3 Inclusion Criteria
15. Disease that has progressed after at least 1 available standard therapy, or for which standard therapy has proven to be ineffective, intolerable, or considered inappropriate, or for which a clinical trial of an investigational agent is a reco

Exclusion criteria

General Exclusion Criteria
Patients who meet any of the following criteria will be excluded from study entry:
1. Inability or unwillingness to swallow pills
1. Inability to comply with study and follow-up procedures
2. Malabsorption syndrome or other condition that would interfere with enteral absorption
3. Pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures biweekly or more frequently
• Indwelling pleural or abdominal catheters may be allowed, provided the patient has adequately recovered from the procedure, is hemodynamically stable and symptomatically improved, and after discussion with the Sponsor.
4. Severe acute or chronic infections, including:
• Uncontrolled acute infection, active infection that necessitates systemic treatment or systemic antibiotic treatment within 2 weeks prior to the first dose of furmonertinib.
• Known history of human immunodeficiency virus (HIV) infection and/or acquired immune deficiency syndrome. Patients with unknown HIV infection status who don*t agree to take HIV test are not eligible.
• Patients with active chronic hepatitis B or with active hepatitis C infection, which includes patients who are hepatitis B surface antigen (HbsAg) positive or hepatitis C virus (HCV) antibody positive at screening, are not eligible until further definite quantitative testing of hepatitis B virus (HBV) DNA (e.g., <= 2500 copies/mL or 500 IU/mL) and HCV RNA tests (e.g., <= lower limit of detection) can conclusively rule out presence of active hepatitis B or C infection that requires treatment.
Note: Patients who are carriers of HBV, with stable HBV infection (e.g., HBV DNA quantitative test showed DNA <= 2500 copies/mL or 500 IU/mL) after medical treatment or with cured hepatitis C are permitted to enroll. If the lower limit of detection of HBV DNA assay in the site is higher than 2500 cps/mL or 500

IU/mL, patients with HBV DNA quantitative test result lower than the lower limit of detection in the site are considered eligible.
5. In the setting of a pandemic or epidemic, screening for active infections should be considered according to local or institutional guidelines or those of applicable professional societies (e.g., American Society of Clinical Oncology [ASCO] or European Society for Medical Oncology [ESMO]).
6. Previous interstitial lung disease (ILD), drug induced ILD, radiation pneumonitis; or active ILD.
7. History of or active clinically significant cardiovascular dysfunction, including the following:
• History of stroke or transient ischemic attack within 6 months prior to first dose of furmonertinib
• History of myocardial infarction within 6 months prior to first dose of furmonertinib
• New York Heart Association Class III or IV cardiac disease or congestive heart failure requiring medication
• Uncontrolled arrhythmias, history of or active ventricular arrhythmia requiring medication
• Coronary heart disease that is symptomatic or unstable angina
8. Mean resting QT interval corrected through use of Fridericia*s formula (QTcF) > 470 ms, obtained from triplicate electrocardiograms (ECGs), using the screening clinic ECG machine-derived QTcF value.
9. Clinically significant prolonged QT interval or other arrhythmia or clinical status considered by investigators that may increase the risk of prolonged QT interval (e.g., complete left bundle branch block, degree III atrioventricular block, second-degree heart block, PR interval > 250 ms, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives, serious hypokalemia, heart failure) or current use of the drugs that may lead to prolonged QT interval.
10. Symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab.
11. Significant traumatic injury or major surgical procedure within 4 weeks prior to Day 1 of Cycle 1.
12. Patients with chronic diarrhea, short bowel syndrome or significant upper gastrointestinal (GI) surgery including gastric resection, a history of inflammatory bowel disease (e.g., Crohn*s disease or ulcerative colitis) or any active bowel inflammation (including diverticulitis).
13. Any other diseases, such as pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of furmonertinib, that may affect the interpretation of the results, or renders the patients at high risk from treatment complications (e.g., uncontrolled hypertension, active bleeding).
14. Treatment with chemotherapy, targeted therapy, biologic therapy, or an investigational agent as anticancer therapy within 3 weeks or 5 elimination half-lives prior to initiation of furmonertinib, whichever is shorter
15. Radiation therapy (other than palliative radiation to bone metastases and

radiation to CNS metastases as described above) as cancer therapy within 4 weeks prior to initiation of furmonertinib.
16. Palliative radiation to bone metastases within 2 weeks prior to initiation of furmonertinib.
17. AEs from prior anticancer therapy that have not resolved to Grade <= 1 except for alopecia or Grade <= 2 peripheral neuropathy.
18. History of other malignancy within 3 years prior to screening, with the exception of patients with a negligible risk of metastasis or death and/or treated with expected curative outcome (such as appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer).
19. Pregnant, breastfeeding, or intending to become pregnant during the study or within 60 days after the final dose of furmonertinib.
• WOCBPs (including those who have had a tubal ligation) must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
20. Known or suspected allergy to furmonertinib or other components of its preparation.
21. Use of a strong CYP3A4 inhibitor within 7 days prior to the first dose of investigational product or a strong CYP3A4 inducer within 21 days prior to the first dose of investigational product.
22. Use of an herbal medicine (e.g., Chinese medicine or traditional Chinese medicine preparation indicated for cancer, or a traditional Chinese medicine or traditional Chinese medicine preparation with adjuvant anticancer effects) within 2 weeks prior to the first dose of furmonertinib, or if herbal medicine is expected to be used during the study.
Stage 2, Cohort 3 (Previously Treated, Locally Advanced or Metastatic NSCLC Patients with EGFR Activating Mutations and Excluding Exon 20 Insertion Mutations and PACC Mutations) Exclusion Criteria.
23. NSCLC patients with a documented EGFR exon 20 insertion mutation by a local test (tumor tissue or blood)
24. NSCLC patients with a documented EGFR PACC mutation by a local test (tumor tissue or blood)
Stage 2, Cohort 4 (Untreated or Previously Treated EGFR-TKI-Naïve, Locally Advanced or Metastatic NSCLC Patients with EGFR PACC Mutations) Exclusion Criteria
25. Prior treatment with any EGFR-TKIs
26. Progression during neoadjuvant or adjuvant therapy (e.g., chemotherapy, radiotherapy, immunotherapy or investigational agents) or within 12 months of completion of above therapies

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	13-04-2023
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Furmonertinib Mesylate
Generic name:	Furmonertinib

Ethics review

Approved WMO Date:	19-12-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-02-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-08-2023

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-05-2024
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	CTIS2023-508349-42-00
EudraCT	EUCTR2021-005831-22-NL
ClinicalTrials.gov	NCT05364073
CCMO	NL82887.041.22