TIGER-2: A Phase 2, Open-Label, Multicenter, Safety and Efficacy Study of Oral CO 1686 as 2nd Line EGFR-Directed TKI in Patients with Mutant EGFR Non-Small Cell Lung Cancer (NSCLC)

Published: 06-11-2014
Last updated: 22-04-2024

Primary Objective* To evaluate the antitumor efficacy of PO single agent CO-1686, as measured by ORR, when administered to patients with EGFR mutated, centrally confirmed T790M positive and T790M negative advanced NSCLC after tumor progression on 1...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Interventional

Summary

ID

NL-OMON44767

Source
ToetsingOnline

Brief title
Tiger-2

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
Non-small cell lungcancer; lungcancer

Research involving
Human

Sponsors and support

Primary sponsor: Clovis Oncology, Inc.
Source(s) of monetary or material Support: Clovis Oncology;Inc

Intervention

Keyword: 2nd Line EGFR-Directed TKI, Non-Small Cell Lung Cancer, Oral CO 1686

Outcome measures

Primary outcome

* ORR according to RECIST Version 1.1 as determined by . For Cohort A, ORR will undergo independent radiology review (IRR) and in Cohort B, scans will be assessed by IRR if needed as a supporting analysis.

Secondary outcome

Secondary Endpoints:

* DR, DCR and PFS according to RECIST Version 1.1 as determined by IRR

* ORR, DR, DCR and PFS according to RECIST Version 1.1 as determined by Investigator Assessment

* OS

* Change from baseline in patient reported outcomes using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ C30), EORTC Quality of Life Questionnaire Lung Cancer module (EORTC QLQ LC13), and the Dermatology Life Quality Index (DLQI)

* Treatment emergent adverse events (AEs), laboratory abnormalities and ECG abnormalities

* Plasma PK parameters for CO-1686 based on sparse sampling

Exploratory Endpoints

* Time-to-treatment failure

* Extra-cranial PFS

* Change from baseline in mutant EGFR levels in ctDNA obtained from plasma

* Positive and negative percent agreement between blood and tissue results for

T790M

* Identify biomarkers associated with response or resistance to CO-1686

Study description

Background summary

In mid-2015, Clovis submitted a New Drug Application for the use of rociletinib in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data is required to approve rociletinib for use outside of a clinical trial. Based on this outcome, Clovis decided to discontinue development of CO 1686 for NSCLC. Patients will be informed of this change in the development plans in an update to the informed consent form for this study. Those patients who continue to derive clinical benefit from study treatment, will be allowed to continue on study at the discretion of the Principal Investigator in an extension phase.
The purpose of this protocol amendment (Amendment 5) is to add a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of assessments for the Extension Phase as well as a complete description of procedures is provided in Appendix C. This schedule replaces all schedules of assessments in Section 9 and should be followed for all patients.

In addition, Amendment 5 (Appendix C) also introduces the availability of NAT2 testing for patients , an indirect indicator of the likelihood of developing hyperglycemia or QTc prolongation. The availability and disclosure of this information to the patients*s treating physician will not affect the monitoring and associated treatment guidelines for these adverse events.

For patients who wish to continue rociletinib treatment post progression, it is important that a full exploration of alternative treatment options between

patients and their treating physicians takes place.
Investigators and their staff are directed to the current Investigator*s Brochure for the most current efficacy and safety data, in which integrated summaries of the latest available data can be found and supersedes all safety and efficacy data in this protocol.

CO-1686 is a novel, potent, small molecule irreversible tyrosine kinase inhibitor (TKI) that selectively targets mutant forms of the epidermal growth factor receptor (EGFR) while sparing wild-type (WT) EGFR.
Activating EGFR mutations are key drivers of NSCLC malignancy in 10% to 15% of patients of European descent and approximately 30% of patients of East Asian descent. Patients with the most common EGFR activating mutations, exon 21 L858R and deletions in exon 19, typically have good responses to therapy with first generation EGFR inhibitors such as erlotinib or gefitinib and also with the second generation inhibitor afatinib. Toxicity associated with erlotinib, gefitinib, and afatinib includes skin rash and diarrhea related to inhibition of the WT EGFR in skin and intestine, respectively.

Despite an impressive initial response to treatment, progression generally occurs after 9-14 months of erlotinib, gefitinib, or afatinib therapy, driven in approximately 60% of cases by a second-site EGFR mutation in exon 20 called T790M (the *gatekeeper* mutation) which mediates resistance to first- and second-generation EGFR inhibitors. There are no approved therapies that target T790M specifically, and standard of care remains cytotoxic chemotherapy. Yu et al reported that T790M positive disease is fatal, with a median overall survival (OS) of less than 2 years.10

Nonclinical data demonstrate that CO-1686 inhibits T790M as well as the common activating mutations (L858R, del19) and has minimal inhibitory activity towards WT EGFR at therapeutic doses. It is anticipated that CO-1686 will promote cell death in tumor cells with the T790M mutation, thus driving objective tumor responses and providing therapeutic benefit in patients who have acquired T790M mediated resistance to first generation EGFR inhibitors. In the first in human study, CO-1686-008, in patients with advanced EGFR mutation positive NSCLC and previous treatment with an EGFR inhibitor, no maximum tolerated dose (MTD) was observed and 3 doses levels, 500 mg twice daily (BID), 625 mg BID, and 750 mg BID, were selected for further clinical evaluation of safety, tolerability and efficacy in the expansion cohorts. Maturing data from this study suggest that patients treated with rociletinib at 500 mg BID and 625 mg BID experience responses that are comparable in frequency, depth and duration, with an overall acceptable safety profile for this advanced cancer patient population. To further describe the risk/benefit profile of the CO 1686 500 mg BID dose, additional patients will be enrolled at a starting dose of 500 mg BID in this study (Cohort B). Response Evaluation Criteria In Solid Tumors (RECIST) responses have been observed across the range of doses studied in Phase 1 with CO-1686, and the current objective response rate (ORR) in patients with T790M positive NSCLC is > 60%. The most common toxicity observed is hyperglycemia,

occurring in approximately 30% of patients, which can usually be readily managed with PO anti hyperglycemic therapy. Adverse events (AEs) typical of WT EGFR inhibition (the combination of rash and chronic diarrhea) have not been observed with CO-1686.

The goals of protocol CO-1686-019 are to evaluate the antitumor efficacy, safety and population pharmacokinetic (POPPK)/pharmacodynamic relationships of PO single agent CO-1686, when administered at the therapeutically active doses of 625 mg BID and 500 mg BID to patients with EGFR mutated, advanced/metastatic NSCLC after failure of 1 previous EGFR directed TKI.
CO-1686 was being developed with a companion diagnostic (Qiagen, United Kingdom) to identify patients whose tumors express activating EGFR mutations as well as the T790M resistance mutation.

Study objective

Primary Objective
* To evaluate the antitumor efficacy of PO single agent CO-1686, as measured by ORR, when administered to patients with EGFR mutated, centrally confirmed T790M positive and T790M negative advanced NSCLC after tumor progression on 1 previous EGFR directed TKI

Secondary Objectives
* To assess clinical efficacy in patients with centrally confirmed T790M positive NSCLC: disease control rate (DCR), duration of response (DR), PFS, and OS following CO-1686 treatment
* To assess quality of life (QoL) by patient reported outcomes (PRO) following CO-1686 treatment
* To evaluate the safety and tolerability of CO-1686
* To determine the pharmacokinetics (PK) of CO 1686 using POPPK methods and explore correlations between PK, exposure, response, and/or safety findings

Exploratory Objectives
* To evaluate clinical benefit of continued CO-1686 treatment following disease progression
* To evaluate concordance of mutant EGFR detection between tissue and plasma and assess CO-1686 mediated alterations in mutant EGFR levels over time using circulating tumor deoxyribonucleic acid (ctDNA) obtained from plasma
* To explore tissue and blood based biomarkers that may be predictive of response or primary resistance to CO-1686 and investigate mechanisms of acquired resistance in the tissue and blood of patients who experience clinical progression during treatment with CO-1686

Study design

This is a Phase 2, single arm, open label, dual cohort, multicenter study

evaluating the safety and efficacy of CO 1686 administered PO BID to patients with previously treated mutant EGFR NSCLC.
Patients will be enrolled into 2 cohorts. Cohort A will enroll approximately 125 eligible patients who are centrally confirmed T790M positive and will be treated at 625 mg BID. Cohort B will be a continuation of the study and will enroll up to approximately 100 eligible patients who will be either centrally confirmed T790M positive or T790M negative. All patients in Cohort B will be treated at a starting dose of 500 mg BID. The priority for study enrollment will be for all T790M positive patients to be enrolled into Cohort A first. Once Cohort A is complete, eligible T790M positive patients will then be enrolled into Cohort B. All eligible T790M negative patients will be enrolled into Cohort B.

Intervention

The study (Cohorts A and B) will consist of a Screening Phase to establish study eligibility and document baseline measurements; an open label Treatment Phase, in which the patient will receive CO- 686 to ascertain efficacy and safety until disease progression as defined by RECIST Version 1.1, clinical tumor progression, or unacceptable toxicity as assessed by the investigator. For patients with clinical progression, radiographic assessment should be performed to document evidence of radiographic progression.

Patients may opt to continue to receive treatment with CO-1686 following radiographic progression, as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR TKIs, if the patient provides additional consent, the investigator believes it is in the best interest of the patient, and the sponsor approves. In general, eligible patients may include those with asymptomatic systemic progression or locally symptomatic progression, such as brain metastases amenable to local treatment, with concomitant asymptomatic systemic progression or continued systemic disease control.

Each 28 day period of treatment will represent 1 cycle, with dosing initiated on Cycle 1 Day 1 (C1D1).
Dosing will be delayed or reduced according to protocol specified toxicity criteria. As mentioned above, patients who provide additional consent may continue to receive treatment with CO 1686 post progression if, in the opinion of the investigator and approved by the sponsor, the patient is still benefitting.

Sparse blood sampling for population PK analyses will be conducted in all patients treated with CO-1686. Serial blood sampling for longitudinal quantitative assessment of ctDNA will be conducted. A central laboratory will confirm presence or absence of the T790M mutation in formalin fixed paraffin embedded (FFPE) tumor tissue prior to study enrollment. Following disease progression on CO-1686, patients who provide additional consent will undergo

tumor biopsy before subsequent line therapy is initiated.

AEs will be collected from the time the first dose of CO-1686 is administered through 28 days after the last dose. Study procedure related AEs that occur after signing of the Informed Consent Form (ICF) and before administration of CO-1686 will also be captured. All patients will be followed at approximately 2 monthly intervals to determine disease progression (if patient discontinues treatment before progression), survival status and subsequent NSCLC therapy until death or sponsor decision, whichever comes first. After discontinuation of protocol specified treatment, subsequent anticancer therapy use will be recorded.

In mid-2015, Clovis submitted a New Drug Application for the use of rociletinib in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data is required to approve rociletinib for use outside of a clinical trial. Based on this outcome, Clovis decided to discontinue development of CO 1686 for NSCLC. Patients will be informed of this change in the development plans in an update to the informed consent form for this study. Those patients who continue to derive clinical benefit from study treatment, will be allowed to continue on study at the discretion of the Principal Investigator in an extension phase.
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Study burden and risks

To date, over 500 patients with NSCLC have received at least one dose of

CO-1686. Commonly reported side effects in these patients, which may have been due to taking the study drug are listed below. However, as CO-1686 is an investigational product, not all side effects are known, and there is a risk that rare or previously unknown side effects may occur.

Common (>20% of patients)
* Nausea
* Hyperglycemia (high blood glucose wich is the same as high levels of sugar in the blood): High blood glucose can cause symptoms such as nausea, vomiting and feeling tired. The patient must tell the doctor if he/she notices any of these symptoms as it could be a sign the blood glucose is increasing. The patient may be asked to take another medicine to control high blood glucose levels.
* Feeling tired
* Loose stools (diarrhea)
* Abnormal heart rhythms, visible on ECG (tracing of the heart rythm), called increase in QT. In severe cases, this can cause changes to the rhythm of the heart; and in rare instances, could result in death. The patient will be carefully monitored in the study for any changes to his/her ECG.

Less Common (5-19% of patients)
* Decrease in appetite
* Muscle spasms
* Vomiting
* Weight loss
* Joint or muscle pain
* Dizziness
* Changes in blood tests that measure how well your kidney and liver are functioning.
* Low blood counts (red blood cells, white blood cells, and platelets).
o A low red blood cell count may make you feel tired or dizzy
o A low white blood cell count puts you at higher risk for infection.
o A low platelet count affects the ability of your blood to clot and could lead to bleeding events

Rare (<5% of patients)
* Constipation
* Headache
* Rash
* Change in sense of taste
* Insomnia (difficulty sleeping)
* Lung inflammation (pneumonitis). Patients taking CO-1686 who developed pneumonitis have recovered, but this event could be very serious and could result in death
* Pancreatitis (inflammation of your pancreas, which in one patient resulted in death)

Some patients who have been taking CO-1686 for an extended period of time have

experienced decreased vision due to clouding of the lens of the eye (cataracts).

In addition to physical examinations including, checking vital signs and the rhythm and rate of the heart, other possible side effects will be regularly monitored for by the study staff when they check the results of the blood tests.

CO-1686 is an experimental drug that may have other side effects that are not known and cannot be predicted at this time. These side effects may be serious. It is important that the patient tells the study staff about any side effects he/she is experiencing, even if he/she does not think they are due to taking the study drug.

Allergic Reactions
Rare or unknown side effects could possibly occur, including life-threatening reactions. As with any drug, it is possible that could have an allergic reaction to CO-1686, such as itching, skin rash, facial swelling, and a severe or sudden drop in blood pressure. The sudden drop in blood pressure may lead to shock with loss of consciousness and/or possible seizures, including the possibility of death.

Blood Sampling
Having blood drawn from a vein in your body may cause some pain, redness, or bruising where the needle is inserted. An infection is also possible, but rare. If the patient feel faint while having your blood drawn, he should sit or lie down to avoid falling.

Procedure(s) to Remove Tumor Tissue
Each type of procedure has some risks and may cause discomfort.

Electrocardiogram (ECG)
The skin may react to the sticky patches that attach the detectors (electrodes) to the chest, wrist and ankles for the ECG. This skin irritation usually disappears when the patches are removed.

CT and MRI Scans
Computed tomography (CT) scans use x-ray radiation. The amount of radiation the patient will receive during a CT scan is small, but the more radiation he receives over the course of his life, the more likely it is that the cells in your body may change or that he develops a new cancer. Some CT scans require the patient to drink a *contrast solution*. It is possible that the contrast solution may cause him to have nausea, vomiting, itching, or skin rash. In rare cases, it may cause the throat to swell and make it hard to breathe. These may be signs of an allergic reaction so tell the study doctor right away if you have any of these side effects. You may have some discomfort from lying still in an enclosed space for a prolonged period of time.
Sometimes a magnetic resonance imaging (MRI) scan is done in patients with allergies to the contrast solution used in a CT scan. An MRI does not use

x-ray radiation, but it takes a little longer and patients sometimes have to lie in a more enclosed space. A contrast agent may be injected into your vein before the scan is done to help the doctor see the tumor more clearly.
X-ray
There is a small possibility that you may require an X- ray during the course of the study.

Pregnancy
Treatment with CO-1686 may involve risks to a fetus, embryo, or unborn child that are currently unknown. The patient cannot participate in this study if she is pregnant or thinking about becoming pregnant. The patient should not nurse (breast feed) a baby while in this study because the study drug may enter breast milk and may possibly harm your child.

Contacts

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US
Scientific
Clovis Oncology, Inc.

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

All patients must meet all of the following inclusion criteria:
1. Histologically or cytologically confirmed metastatic or unresectable locally advanced NSCLC
2. Documented evidence of a tumor with 1 or more EGFR mutations excluding exon 20 insertion
* Disease progression confirmed by radiologic assessment while receiving treatment with the first single agent EGFR TKI (eg, erlotinib, gefitinib, afatinib, or dacomitinib)
o EGFR TKI treatment discontinued * 30 days prior to planned initiation of CO 1686 (the washout period for an EGFR inhibitor is a minimum of 3 days)
o No intervening treatment between cessation of single agent EGFR TKI and planned initiation of CO 1686
o Previous treatment with * 1 prior chemotherapy (excluding prior neo adjuvant or adjuvant chemotherapy or chemoradiotherapy with curative intent)
o Any toxicity related to prior EGFR inhibitor treatment must have resolved to Grade 1 or less
* Central laboratory confirmation of the presence of the T790M mutation in tumor tissue in Cohort A and the presence or absence of the T790M mutation in tumor tissue in Cohort B. Centrally indeterminate, unknown or invalid specimens are not acceptable. Biopsy material obtained from either primary or metastatic tumor tissue must have been obtained (and sent to the central laboratory) within 60 days prior to dosing study drug but following disease progression on the first EGFR TKI.
3. Measureable disease according to RECIST Version 1.1
4. Life expectancy of at least 3 months
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
6. Age * 18 years (in certain territories, the minimum age requirement may be higher, eg age * 20 years in Japan and Taiwan)
7. Adequate hematological and biological function, confirmed by the following laboratory values:
* Bone Marrow Function
o Absolute neutrophil count (ANC) * 1.5 x 109/L
o Platelets > 100.0 × 10 9/L
o Hemoglobin * 9 g/dL (or 5.6 mmol/L)
* Hepatic Function
o Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) * 3 × upper limit of normal (ULN); if liver metastases, * 5 × ULN
o Bilirubin * 2 × ULN
* Renal Function
o Serum creatinine * 1.5 × ULN
* Electrolytes
o Potassium and magnesium within normal range. Patients may receive supplements to meet this requirement
8. Written consent on an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved ICF prior to any study specific evaluation

Exclusion criteria

Any of the following criteria will exclude patients from study participation:
1. Documented evidence of an exon 20 insertion activating mutation in the EGFR gene
2. Active second malignancy; i.e. patient known to have potentially fatal cancer present for which he/she may be (but not necessarily) currently receiving treatment
* Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/or bone marrow transplant > 2 years prior
3. Known pre existing interstitial lung disease
4. Cohort A only: Patients with leptomeningeal carcinomatosis are excluded. Other central nervous system (CNS) metastases are only permitted if treated, asymptomatic, and stable (not requiring steroids for at least 4 weeks prior to the start of study treatment). Cohort B only: Patients with CNS metastases or leptomeningeal carcinomatosis are excluded.
5. Treatment with prohibited medications (eg, concurrent anticancer therapy including other chemotherapy, radiation, hormonal treatment [except corticosteroids and megesterol acetate], or immunotherapy) * 14 days prior to treatment with CO 1686
6. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval and the treatment cannot be either discontinued or switched to a different medication before starting CO 1686
* see http://crediblemeds.org/ for a list of QT prolonging medications (includes all medication under categories of Known, Possible and Conditional risk of Torsades de Pointes)
7. Prior treatment with CO 1686, or other drugs that target T790M positive mutant EGFR with sparing of wild type EGFR eg, AZD9291, HM61713, TAS 121
8. Any of the following cardiac abnormalities or history:
* Clinically significant abnormal 12 lead ECG, QT interval corrected using Fridericia*s method (QTCF) > 450 msec
* Inability to measure QT interval on ECG
* Personal or family history of long QT syndrome
* Implantable pacemaker or implantable cardioverter defibrillator
* Resting bradycardia < 55 beats/min
9. Nonstudy related surgical procedures * 7 days prior to administration of CO 1686. In all cases, the patient must be sufficiently recovered and stable before treatment administration
10. Females who are pregnant or breastfeeding
11. Refusal to use adequate contraception for fertile patients (females and males) while on treatment and for 12 weeks after the last dose of CO 1686
12. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (eg, substance abuse, uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism)
13. Any other reason the investigator considers the patient should not participate in the study

Study design

Design

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):	19-02-2015
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CO-1686 125 mg
Generic name:	CO-1686
Product type:	Medicine
Brand name:	CO-1686 250 mg
Generic name:	CO-1686

Ethics review

Approved WMO Date:	06-11-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	11-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2013-005532-23-NL
ClinicalTrials.gov	NCT02147990
CCMO	NL50089.029.14