A Randomized, Controlled Phase 2 Study Evaluating LY2875358 plus Erlotinib versus Erlotinib as First-Line Treatment in Metastatic Non-Small Cell Lung Cancer Patients with Activating EGFR Mutations Who Have Disease Control after an 8-Week Lead-In Treatment with Erlotinib

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The primary objective of this study is to compare PFS with LY2875358 plus erlotinib therapy with erlotinibmonotherapy as first-line treatment in metastatic NSCLC patients with activating EGFR mutations who havedisease control after an 8-week lead-in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON44916

Source
ToetsingOnline

Brief title
I4C-MC-JTBB(a)

Condition

- Respiratory tract neoplasms

Synonym
non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly Nederland BV
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: acquired resistance, EGFR mutations, erlotinib, non-small cell lung cancer

Outcome measures

Primary outcome

Efficacy:

Primary Objective:

Progression-free survival (PFS): The time from the date of study randomization

to the date of first observation of

objective radiographic progression or death from any cause as defined by RECIST

1.1 (Eisenhauer et al. 2009)

Secondary outcome

Secondary Objectives:

* Change in tumor size (CTS): The change in tumor size from baseline to the

measurement with the smallest

tumor size during the study

* Overall response rate (ORR): The proportion of patients who exhibit a

confirmed CR or PR relative to baseline

as defined by RECIST 1.1 (Eisenhauer et al. 2009)

* Time to progressive disease (TTPD): The time from the date of study

randomization to the date of first

observation of objective progression

* Duration of response (DoR): The time from the date of first evidence of a confirmed CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier

* Disease control rate (DCR): The proportion of patients in the analysis population who exhibit SD or a confirmed CR or PR relative to baseline during the study; response is defined by RECIST 1.1 (Eisenhauer et al. 2009)

* Overall survival (OS): The time from randomization until death for any reason

Health Outcomes:

Patient symptoms and QoL will be assessed using the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-LC13.

Safety:

Adverse events (AEs), serious adverse events (SAEs), physical examinations, vital sign measurements, clinical laboratory evaluations, treatment discontinuation due to toxicity, and safety will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Pharmacokinetics: The parameters for erlotinib will include steady-state maximum and minimum concentration

(Css,max and Css,min) and area under the concentration-time curve during the dosing interval at steady state (AUC*,ss). The parameters for LY2875358 may include systemic clearance (CL), volume of distribution (V), Css,min, and target- mediated drug disposition (TMDD) model parameters, such as receptor mediated clearance, non-receptor-mediated clearance, volume of the central compartment, and volume of the peripheral compartment.

Exploratory Biomarkers:

Tumor tissue and blood samples will be collected and analyzed for exploratory biomarker related to the MET and EGFR signaling pathway or NSCLC biology. Tumor samples may be analyzed for, including, but not necessarily limited to MET protein expression, MET and EGFR amplification, HGF protein expression, and EGFR mutation (EGFRmt) status. Blood samples may be analyzed for, including, but not necessarily limited to, circulating levels of HGF and the extracellular cleaved domain of MET (MET ECD). Blood biomarker levels from baseline, leadin study period and the randomized study period may be compared. In addition the time course of blood biomarker levels during the study randomized study period and PK/PD

biomarker

relationship may be evaluated.

Study description

Background summary

Study I4C-MC-JTBB will test the hypothesis whether the addition of LY2875358 to standard-of care
erlotinib delays the emergence of acquired resistance to erlotinib as measured by
progression-free-survival in first-line non-small cell lung cancer patients with activating EGFR
mutations who have disease control after an 8-week lead-in treatment with erlotinib
monotherapy.

Study objective

The primary objective of this study is to compare PFS with LY2875358 plus erlotinib therapy with erlotinib
monotherapy as first-line treatment in metastatic NSCLC patients with activating EGFR mutations who have
disease control after an 8-week lead-in treatment with erlotinib monotherapy.

Study design

Study I4C-MC-JTBB (JTBB) is a multicenter, randomized, open-label, parallel, controlled, phase 2 study in
metastatic NSCLC patients (stage IV) with activating EGFRmt who have disease control after an 8-week lead-in
treatment with erlotinib. Patients with radiographic disease control at the end of the erlotinib lead-in study period
will be randomized to receive LY2875358 plus erlotinib or erlotinib monotherapy. It is the aim of the study to
compare the antitumor activity and safety of both treatment regimens as first-line treatment in the study population.
Study JTBB will test the hypothesis whether the addition of LY2875358 to standard-of-care erlotinib delays the
emergence of treatment resistance to erlotinib (*acquired resistance*) as measured by PFS.
Approximately 179 patients will be enrolled in Study JTBB. Upon registration and completion of screening

procedures, all eligible patients will be enrolled and will receive a lead-in treatment with erlotinib monotherapy
(150 mg once daily [QD]). Only patients without radiographic or clinical disease progression at the end of the 8-
week erlotinib lead-in study period will be randomized on a 1:1 basis to receive either:
Investigational Arm A:
* LY2875358 750-mg flat dose as a 1.5-hour infusion (Days 1 and 15 of a 28-day cycle)
* Erlotinib 150 mg QD (28-day cycle)
Control Arm B:
* Erlotinib 150 mg QD (28-day cycle)
A dynamic randomization procedure will be used to minimize imbalance between treatment arms according to the
following factors:
* MET expression status: MET high vs. MET low vs. indeterminable
* Eastern Cooperative Oncology Group (ECOG) performance status at the end of the erlotinib lead-in
period: 0 vs. 1 vs. 2
* Response at the end of the erlotinib lead-in period: stable disease (SD) vs. partial response (PR) vs.
complete response (CR) (ie, unconfirmed response according to Response Evaluation Criteria in Solid
Tumors [RECIST] version 1.1)
* Ethnicity: East Asian vs. non-east Asian
Patients randomized to the erlotinib monotherapy arm (Arm B) will be offered at the time of objective disease
progression to receive treatment with LY2875358 plus erlotinib at the dose and schedule outlined for Arm A.

Intervention

Test Product, Dosage, and Mode of Administration:
LY2875358 (750-mg flat dose intravenous [IV] every 2 weeks [Q2W])

Planned Duration of Treatment: approximately 14 months
Lead-In Period: 8 weeks (±1 week)
Study Period: until disease progression or unacceptable toxicity occurs (or both)
Short-Term Follow-Up Period (post discontinuation): approximately 30 days
Long-Term Follow-Up Period (starts 1 day after short-term follow-up): until death or study completion

Reference Therapy, Dose, and Mode of Administration: Erlotinib 150 mg QD orally administered

Study burden and risks

There are risks involved with the study drug. There are also risks involved with the treatment. The study drug and the combination with the standard treatment can also involve other, unknown risks. Risks involved with the study drug, erlotinib and the study procedures are listed in the subject information sheetThe patients who participate have a form of metastatic lung cancer with little limited survival prognosis. Drugs that can extend their life and improve the quality of life are needed. Objective is to find out whether the addition of LY2875358 to
standard-of-care erlotinib delays the emergence of acquired resistance to erlotinib.

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

[1] Have a histologically or cytologically confirmed diagnosis of metastatic Stage IV NSCLC at the time of study entry (American Joint Committee on Cancer Staging Criteria for NSCLC, Seventh Edition; Edge et al. 2009).;[2] Have at least 1 measurable lesion whose presence is assessable using standard techniques by RECIST version 1.1 (Eisenhauer et al. 2009). For patients with prior radiation therapy, measurable lesions must be outside a previous radiotherapy field if they are the sole site of disease, unless disease progression has been documented at that site since radiation. ;[3] Have molecular evidence of an EGFRmt known to be associated with drug sensitivity (G719X, exon 19 deletion, L858R, L861Q; further activating EGFRmt may be included in the future if supported by scientific evidence after discussion with the sponsor). This determination should be made from a NSCLC tumor sample based on testing with an EGFRmt assay (either a regulatory approved assay or by a local assay validated in a local laboratory according to institutional guidelines and local standard of care).;[4] Availability of adequate tumor-derived material from a biopsy or surgery (tumor blocks or slides) for analysis of MET expression status (needed for stratification) and exploratory biomarkers analysis. ;[5] Have a performance status of =<2 on the Eastern Cooperative Oncology Group (ECOG) scale.;[6] Have not received previous systemic chemotherapy, systemic therapy with biologics, or molecular-targeted therapy for Stage IV NSCLC. Patients who received chemotherapy as neoadjuvant or adjuvant therapy for early-stage NSCLC disease and completed therapy at least 6 months prior to enrollment are eligible. ;[7] Have adequate organ function, as demonstrated by the following parameters:
• Hematologic: Absolute neutrophil count (ANC) *1.5 × 109/L, platelets *100 × 109/L, and hemoglobin *8 g/dL
• Hepatic: Bilirubin <=1.5 × upper limits of normal (ULN); albumin >=25 g/L; alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) <=2.5 × ULN or <=5 × ULN in patients with hepatic metastases. NOTE: Patients with bone metastases and isolated elevation of ALP and patients with a documented Gilbert syndrome and isolated elevation of bilirubin are eligible.
• Renal: Serum creatinine level <=1.5 × ULN; or calculated serum creatinine clearance >=50 mL/min according to the method of Cockcroft and Gault;[8] Patients who require oral anticoagulants (eg, warfarin) are eligible provided there is increased vigilance with respect to the monitoring of the patient's international normalized ratio (INR), according to investigator judgment. If medically appropriate and the treatment is available, the investigator may also consider switching these patients to low-molecular-weight heparin or oral factor Xa inhibitors, with which an interaction with LY2875358 or erlotinib is not expected.;[9] Are men or women at least 18 years of age at the time of screening.;[10] Eligible patients of reproductive potential (both sexes) must agree to use adequate contraceptive methods (hormonal or barrier methods) during the study period and at least 12 weeks after the last dose of study therapy, or longer if required by local regulations.;Women of child-bearing potential must test negative for pregnancy within 7 days prior to enrollment based on a serum pregnancy test and must also not be breastfeeding.;[11] Are able to swallow tablets.;[12] Have an estimated life

expectancy of at least 12 weeks in the judgment of the investigator.;[13] Patients must have given written informed consent prior to any
study-specific procedures and be willing to make themselves available
for the duration of the study and follow study procedures.

Exclusion criteria

[14] Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product or nonapproved use of a drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.;[15] Have previously completed or withdrawn from this study or any other study investigating LY2875358. (This exclusion criterion does not apply to patients who are rescreened prior to enrollment.);[16] Have a serious concomitant systemic disorder (eg, active infection including human immunodeficiency virus [HIV], or significant cardiac disease (eg, history of New York Heart Association class >=3 disease, unstable angina, or myocardial infarction in 6 months prior to study drug administration) that, in the opinion of the investigator, would compromise the patient*s ability to adhere to the protocol.;[17] Have interstitial pneumonia or interstitial fibrosis of the lung that, in the opinion of the investigator, could compromise the patient or the study treatment with erlotinib.;[18] Have pleural effusion, pericardial fluid, or ascites requiring drainage every other week or more frequently. NOTE: Patients with a permanently implanted catheter system in place for repeated draining of pleural effusions or ascites (eg, "PleurX" system) are eligible.;[19] Have a history of another malignancy except for basal or squamous cell skin cancer, in situ carcinoma of the cervix, other noninvasive cancers that in the judgment of the investigator and sponsor may not affect the interpretation of the study results or other solid tumors treated curatively and without evidence of recurrence for at least 3 years prior to the study.;[20] Have any major surgery less than 2 weeks prior to initiation of study treatment. ;[21] Have any condition (eg, psychological, geographical.) that does not permit compliance with study and follow-up procedures or suggests that the patient is, in the investigator*s opinion, not an appropriate candidate for the study. ;[22] Are pregnant or lactating women. ;The following Exclusion Criteria [23]-[24] will be assessed at the end of the 8-week lead-in study period with erlotinib monotherapy: ;[23] Have radiographic or clinical progression of disease (according to RECIST version 1.1) at the end of the 8-week erlotinib lead-in study period. ;[24] Have CNS metastasis (screening not required) except:
Patients with CNS metastases treated with surgery and/or radiation are eligible for randomization if they are, at the end of the 8-week erlotinib lead-in study period, either or both of the following:
• Clinically stable with regard to neurologic function and off corticosteroids after cranial irradiation (ie, whole-brain radiation therapy, focal radiation therapy, or stereotactic radiosurgery) at least 3
weeks prior to randomization, or after surgical resection performed at least 28 days prior to randomization. The patient may have no evidence of Grade >=1 CNS hemorrhage based on pretreatment magnetic resonance imaging (MRI) or IV contrast-enhanced computed tomography (CT) performed within 3 weeks prior to randomization
• asymptomatic with regard to neurologic function and, if taking corticosteroids, must be on

a stable dose for >=2 weeks prior to randomization.
Patients with CNS metastases not treated with surgery and/or radiation are eligible for randomization if they are at the end of the 8-week erlotinib lead-in study period asymptomatic and clinically stable with regard to neurologic function and not requiring steroids or anticonvulsants to control CNS metastases-related symptoms.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-04-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LY2875358
Generic name:	LY2875358

Ethics review

Approved WMO

Date:	02-05-2013
Application type:	First submission

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-08-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-09-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-09-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	23-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-05-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2012-005476-33-NL
CCMO	NL44373.100.13