A Randomized, Open-Label Phase 2 Study Evaluating LY2875358 Plus Erlotinib and LY2875358 Monotherapy in MET Diagnostic Positive NSCLC Patients with Acquired Resistance to Erlotinib

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The primary objective of this study is to evaluate the overall response rate (ORR) of LY2875358 plus erlotinib therapy and LY2875358 monotherapy in patients with met proto-oncogene (hepatocyte growth factor receptor) (MET) diagnostic positive (MET...

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

Summary

ID

NL-OMON38762

Source
ToetsingOnline

Brief title
I4C-MC-JTBC (219-726)

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
non small cell lung cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Erlotinib, MET positive, non small cell lung cancer

Outcome measures

Primary outcome

ORR: The proportion of patients who exhibit a confirmed complete response (CR) or partial response (PR) relative to baseline as defined by RECIST 1.1 (Eisenhauer et al. 2009)

Secondary outcome

Secondary Objectives:

• Progression-free survival (PFS): The time from the date of study enrollment (randomization) to the date of first observation of objective progression or death from any cause

• Time to progressive disease (TTPD): The time from the date of study enrollment (randomization) to the date of first observation of objective progression

• Change in tumor size (CTS): The change in tumor size from baseline measurement to the measurement with the smallest tumor size during the study

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

• 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. Response is defined by RECIST 1.1 (Eisenhauer et al. 2009).

• Overall survival (OS): defined to be the time from randomization until death for any reason.

Health Outcomes:

Patient symptoms, QoL, and health status will be assessed using the European Organisation for the Research and Treatment of Cancer (EORTC) questionnaires QLQ-C30, QLQ-LC13, and EuroQol EQ-5D.

Safety:

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

Pharmacokinetic:

The parameters for erlotinib will include steady-state maximum and minimum concentrations (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 may be collected and analyzed for exploratory biomarkers related to the MET and EGFR signaling pathway or NSCLC biology. Tumor samples may be analyzed for biomarkers including, but not necessarily limited to, MET protein expression, MET and EGFR amplification, HGF protein expression, and EGFRmt status (including T790M). Blood samples may be analyzed for parameters including, but not necessarily limited to, circulating levels of HGF and the extracellular cleaved domain of MET (MET ECD). Blood biomarker levels from the study treatment period may be compared with baseline levels. In addition, the time course of blood biomarker levels during the study treatment period, the PK/PD biomarker relationship may be evaluated.

Study description

Background summary

Study I4C-MC-JTBC (JTBC) will test the hypothesis whether acquired resistance to erlotinib in MET diagnostic-positive non-small cell lung cancer (NSCLC) patients can be overcome by treatment with LY2875358 plus erlotinib as measured by overall response rate (ORR). The study will also explore whether LY2875358 monotherapy has clinical activity in this patient population as measured by ORR.

Study objective

The primary objective of this study is to evaluate the overall response rate (ORR) of LY2875358 plus erlotinib therapy and LY2875358 monotherapy in patients with met proto-oncogene (hepatocyte growth factor receptor) (MET) diagnostic

positive (MET diagnostic [+]) non-small cell lung cancer (NSCLC) and acquired resistance to erlotinib.

As a co-primary objective, this study will evaluate the ORR of LY2875358 plus erlotinib therapy and LY2875358 monotherapy in the subpopulation of patients with MET-high expression status based on their post-erlotinib progression NSCLC tumor sample.
The secondary objectives of the study are as follows:
• To evaluate efficacy variables:
• Progression-free survival (PFS)
• Time to progressive disease (TTPD)
• Change in tumor size (CTS)
• Disease control rate (DCR)
• Duration of response (DoR)
• Overall survival (OS)
• To evaluate patient-reported outcome measures
• To characterize the safety and tolerability of LY2875358 when administered in combination with erlotinib or as monotherapy
• To evaluate pharmacokinetics of LY2875358 when administered in combination with erlotinib and as monotherapy
• To evaluate incidence and serum levels of antitherapeutic antibodies against LY2875358

The exploratory objectives for this study are as follows:
• To evaluate the primary objective and all secondary objectives in the subpopulation of patients with MET-high expression status and known activating EGFRmt based on their post-erlotinib progression NSCLC tumor sample
• To evaluate tumor tissue and blood for further biomarkers related to the MET and EGFR signaling pathway or NSCLC biology (which may include but is not necessarily limited to MET protein expression, MET and EGFR amplification, HGF protein expression, EGFRmt status [including T790M]) and their potential association with the objectives of the study (including pharmacokinetic/pharmacodynamic [PK/PD] biomarker relationship).
• To evaluate central nervous system (CNS) PFS and extra-CNS PFS

Study design

Study I4C-MC-JTBC (JTBC) is a multicenter, randomized, open-label, parallel, uncontrolled, Phase 2 study evaluating LY2875358 plus erlotinib versus LY2875358 monotherapy in MET diagnostic (+) NSCLC patients with acquired resistance to erlotinib. For enrollment, only patients with metastatic (Stage IV) and MET diagnostic (+) NSCLC tumor samples as determined by the Study JTBC central laboratory will be eligible. Patients must have documented radiographic progression while on continuous treatment with erlotinib

monotherapy within at least the last 28 days (*acquired resistance to erlotinib*) and have either an activating EGFRmt or have had objective clinical benefit from the most recent erlotinib therapy. Patients may not have received any other intervening systemic therapy since the most recent radiographic progression except erlotinib, which is allowed to be continued at the investigator*s discretion until initiation of study treatment. Patients who stopped erlotinib treatment upon progression will need to initiate JTBC study treatment no later than 28 days after discontinuing erlotinib administration. Study JTBC will test the hypothesis whether acquired treatment resistance to erlotinib can be overcome by treatment with LY2875358 plus erlotinib as measured by ORR. The study will also explore whether LY2875358 monotherapy has clinical activity in this patient population. Approximately 100 patients will be enrolled in Study JTBC. Upon registration and completion of screening procedures, all eligible patients will be randomized on a 3:1 basis to receive either:
Investigational Arm A:
o LY2875358 750-mg dose as 1.5-hour infusion (Days 1 and 15 of a 28-day cycle)
o Erlotinib 150 mg (daily on a 28-day cycle)
Investigational Arm B:
o LY2875358 750-mg dose as 1.5-hour infusion (Days 1 and 15 of a 28-day cycle)
Randomization will be stratified according to:
• Eastern Cooperative Oncology Group (ECOG) performance status: 0 vs. 1 vs. 2
• Number of prior lines of chemotherapy: 0 vs. 1 vs. >=2

Intervention

Test Product, Dosage, and Mode of Administration:
• LY2875358 at a 750-mg dose given on Days 1 and 15 of a 28-day cycle, provided lyophilized in vials for intravenous (IV) administration
• Erlotinib at a dose of 150 mg daily on a 28-day cycle, as tablets to be administered orally

Planned Duration of Treatment: approximately 6 months
Treatment period: Until disease progression or unacceptable toxicity occurs (or both)
Short-term follow-up period (post discontinuation): 30 days
Long-term follow-up period (starts 1 day after short-term follow up): until death or study completion

Study burden and risks

There are risks involveld with the study drug. There are also risks involved with the treatment. The study durg and the combination with the standard treatment can also involve other, unknown risks. Risks involved wit hthe study drug erlotinib and the study procedures are listed in the risk appendix of the patient information form. The patients who participate have a form of

metastatic lung cancer with limited survival prognosis. Drugs that can extend their life and improve quality fo life are needed.

Contacts

Public
Eli Lilly

Lilly Corporate Center 1
Indianapolis IN46285
US
Scientific
Eli Lilly

Lilly Corporate Center 1
Indianapolis IN46285
US

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, 7th edition; Edge et al. 2009) and must be, in the judgment of the investigator, an appropriate candidate for experimental therapy.;[2] Have at least 1 measurable extra-CNS lesion whose presence is assessable using standard techniques by the Response Evaluation Criteria in Solid Tumors (RECIST 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 documented radiographic progression of disease (use RECIST version 1.1 as guidance for definition of progression) while on continuous treatment with erlotinib monotherapy within at least the last 28 days (minimum >=100 mg erlotinib/d). Patients may not have received any other intervening systemic therapy since most recent radiographic progression on erlotinib except erlotinib which is allowed to be continued at the investigator*s discretion until initiation of study treatment. Patients who stopped erlotinib treatment upon progression will need to initiate JTBC study treatment no later than 28 days after discontinuing erlotinib. ;NOTE: Patients whose disease progresses only in the central nervous system (CNS) are not eligible.;[4] Have either one or both of the following:;• Molecular evidence of an activating EGFRmt known to be associated with EGFR TKI 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) from a tumor sample based on testing with a validated EGFRmt assay. ;• Objective clinical benefit from most recent erlotinib treatment as defined by either documented partial or complete response or stable disease >=6 months as defined by RECIST version 1.1 in absence of radiographic progression after initiation of erlotinib. Patients with only symptomatic improvement while on erlotinib but no corresponding evidence of radiographic stability of disease are not eligible.;[5] Determined to be MET diagnostic (+) as determined by the Study JTBC central laboratory based upon testing of a NSCLC tumor sample obtained at any time (ie. time of diagnosis of NSCLC or any time beyond). ;[6] Availability of a tumor sample taken from an extra-CNS lesion, or patient willingness to undergo a tumor biopsy of an extra-CNS lesion, post-erlotinib progression. The tumor sample should be taken from a progressing lesion on erlotinib whenever possible. ;[7] Performance status of <=2 on the Eastern Cooperative Oncology Group (ECOG) scale.;[8] Have adequate organ function, as demonstrated by: ;• Hematologic: Absolute neutrophil count (ANC) *1.5 × 109/L, platelets *100 × 109/L, and hemoglobin *8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin until 14 days after the erythrocyte transfusion.;• Hepatic: bilirubin <=1.5 times upper limits of normal (ULN), albumin >=25 g/L alkaline phosphatase (ALP), and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=2.5 times ULN or <=5 times ULN in patients with hepatic metastases.;• Renal: Serum creatinine level <=1.5 × ULN or calculated serum creatinine clearance >=50 mL/min, according to the method of Cockcroft and Gault.;[9] Patients who require oral anticoagulants (eg. warfarin) are eligible provided there is increased vigilance with respect to the monitoring of 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, with which an interaction with LY2875358 or erlotinib is not expected.;[10] Are male or female and at least 18 years old (or older if required by local law or regulations) at the time of screening.;[11] 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. ;[12] Are able to swallow tablets.;[13] Have an estimated life expectancy of at least 12 weeks in the judgment of the investigator.;[14] Have given written informed consent/assent prior to any study-specific procedures and are willing to make themselves available for the duration of the study and are willing to follow study procedures.

Exclusion criteria

[15] 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.;[16] Have previously completed or withdrawn from this study (exclusive patients who are rescreened prior to enrollment) or have been treated previously with LY2875358 or any other MET-targeting experimental therapeutic (including but not limited to: XL184, ARQ197, MetMab, crizotinib). There are no limitations to systemic therapies regimens (including any EGFR-directed therapies) prior to the most recent progression on erlotinib monotherapy.;[17] Have a serious concomitant systemic disorder (eg, active infection including human immunodeficiency virus), or significant cardiac disease (eg, history of New York Heart Association class >=3, unstable angina, 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.;[18] Have interstitial pneumonia or interstitial fibrosis of the lung, which, in the opinion of the investigator, could compromise the patient or the study treatment with erlotinib.;[19] Have pleural effusion, pericardial fluid, or ascites requiring drainage every other week or more frequently.;[20] have a history of another malignancy except for basal or squamous cell skin cancer and/or in situ carcinoma of the cervix, or other solid tumors treated curatively and without evidence of recurrence for at least 3 years prior to the study.;[21] Have major surgery less than 2 weeks prior initiation of study treatment therapy. ;[22] Have any condition (eg, psychological, geographical) that does not permit compliance with study and follow-up procedures, or patient is, in the investigator*s opinion, not an appropriate candidate for the study.;[23] Pregnant or lactating women.;[24] Have symptomatic CNS metastasis (baseline computer tomography [CT] or magnetic resonance imaging [MRI] of the brain required in all patients. For those patients with known CNS metastases ongoing CNS surveillance using the same modality is required at half the frequency as extra-CNS imaging).;Patients with asymptomatic CNS metastases are eligible if they are clinically stable with regard to neurologic function and either untreated and not requiring steroids or anticonvulsants to control CNS metastases related symptoms or are off steroids after cranial irradiation (whole-brain radiation therapy, focal radiation therapy, and stereotactic radiosurgery) at least 2 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 or IV contrast-enhanced CT (performed within 2 weeks prior to randomization).

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:	Recruitment stopped
Start date (anticipated):	13-10-2013
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LY2875358
Generic name:	na
Product type:	Medicine
Brand name:	Tarceva
Generic name:	Erlotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	17-05-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	12-06-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	01-11-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-11-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-09-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2015
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	EUCTR2012-005477-31-NL
CCMO	NL44552.056.13