A phase I/II, multicenter, open-label study of EGFRmut-TKI EGF816, administered orally in adult patients with EGFRmut solid malignancies (CEGF816X2101)

Published: 23-07-2015
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Phase I partPrimary:* Determine the maximum tolerated dose (MTD) or the recommended phase II dose (RP2D).Secondary:* Safety and tolerability, * ORR, duration of response (DOR), disease control rate (DCR), progression free survival (PFS) and time to...

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

Summary

ID

NL-OMON52991

Source
ToetsingOnline

Brief title
CEGF816X2101

Condition

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

Synonym
non-small cell lung cancer; lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: EGF816, EGFR-TKI, mutation

Outcome measures

Primary outcome

Phase I: MTD or RP2D

Phase II: ORR.

Secondary outcome

Phase I:

Adverse events, ORR, DOR, DCR, PFS, TTR and PK characteristics of EGF816 and

metabolite LMI258. Determination of EGFR pathway induction.

Phase II:

Adverse events, ORR, DOR, DCR, PFS, TTR and OS PK characteristics of EGF816 and

metabolite LMI258.

Study description

Background summary

Based on preclinical data for EGF816 and the known clinical activity of other 3rd-generation epidermal growth factor receptor (EGFR) inhibitors, it is expected that EGF816 would exhibit to significant antitumor activity in non-small cell lung cancer (NSCLC) patients harboring the activating EGFR mutations (e.g., L858R and ex19del) and/or the acquired/resistant *gatekeeper* T790M mutation while sparing wild-type (WT) EGFR.
In the Phase I part (dose-escalation) of this study the maximum tolerated dose

(MTD) or recommended phase II dose (RP2D) has been determined and the preliminary antitumor activity has been determined of single-agent EGF816 in adult patients with stage IIIB/IV NSCLC harboring a documented EGFR T790M mutation. The Phase I part will be conducted in NL with 2 centers, the EMC and the AvL.
NL will participate in the Phase II part of the study with 3 centers: EMC, AVL en MUMC. The purpose of the Phase II part is to evaluate the efficacy and safety of single-agent EGF816 in the MTD/RP2D dose determined in Phase I in adult patients with stage IIIB/IV NSCLC whose tumors harbor specific EGFR mutations. The expansion and the phase II part will consist of 1 group (The patients must not have received any prior systemic antineoplastic therapy in the advanced setting (NSCLC stage IIIB or IV). However, patients who have failed no more than 1 cycle of systemic
antineoplastic therapy in the advanced setting are allowed. Note: Neo-adjuvant and adjuvant systemic therapies will be counted as 1 prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant/adjuvant systemic therapy.

Study objective

Phase I part
Primary:
* Determine the maximum tolerated dose (MTD) or the recommended phase II dose (RP2D).

Secondary:
* Safety and tolerability,
* ORR, duration of response (DOR), disease control rate (DCR), progression free survival (PFS) and time to response (TTR), pharmacokinetics (PK) properties of EGF816 and metabolite LMI258. Determination of EGFR pathway induction.

Phase II part
Primary:
* To evaluate the antitumor activity of EGF816 as measured by overall response rate (ORR) determined by Blinded Independent Review Committee.
Secondary:
* Safety and tolerability, ORR, duration of response (DOR), disease control rate (DCR), progression free survival (PFS) and time to response (TTR), overall survival (OS), pharmacokinetics (PK) properties of EGF816 and metabolite LMI258.

Study design

Multicenter phase I/II open-label dose-escalaton (phase I) and dose-expansion (phase II) study.
Study treatment: EGF816 capsules or tablets once daily. Continuous dosing.

Cycles of 4 weeks.
Treatment until disease progression or unacceptable side effects. Patients who discontinue study treatment for any reason other than disease progression will be followed up for progression of disease and all patients will be followed for survival.
Approx. 40 subjects for Phase II part and at least 180 for the phase I part.
Total at least 220.
NL will participate in the phase II part.

Intervention

Treatment with EGF816.

Study burden and risks

Risk: Adverse effects of EGF816.

Phase I
Burden: Cycles of 4 weeks. Cycle 1: 6 visits, Cycle 2: 5 visits, from cycle 3 onwards: 2 visits. Duration mostly 2 hours. 2-3 visits up to 8 hours.
Physical examination: 4x during cycle 1 en 2, 1x/cycle.
Blood tests (10-15 ml/occasion): cycle 1 and 2: 4x. Afterwards 2x per cycle.
Extra for biomarkers (20-30 ml/occasion): every 2nd cycle. Extra for PK (2ml/sample): 3 days with 8 samples in 8 h and 6 days with 1 sample.
Pregnancy test: 3-5 times.
HCV en HBV tests: at least 1x
Tumor measurements: every 8 weeks.
ECG: during 5 days (there off 2 days with 2 ECGs in 2 h). In some centers extended ECG monitoring: 2 days with 5 ECGs in 8 h (= PK days; instead of 2 ECGs in 2 h), 1 day with 2 ECGs in 2 h. 3 days with 1 ECG.
Tumorbiopsie: 1-2 obligated in phase I. 2x optional.

Phase II
Burden: Cycles of 4 weeks. Cycle 1: 5 visits, Cycle 2: 3 visits from cycle 3 onwards: 2 visits. Duration mostly 2 hours. 2-3 visits up to 8 hours.
Physical examination: once/cycle.
Blood tests (10-15 ml/occasion): once per cycle. Extra for biomarkers (20-30 ml/occasion): every third cycle. Extra for PK (2ml/sample): 3 days with 8 samples in 8 h and 6 days with 1 sample.
Pregnancy test: 3-5 times.
HCV en HBV tests: at least 1x
Tumor measurements: every 8 weeks.
ECG: during 8 days, 2 days with 5 ECGs in 8 h, 1 day with 2 ECGs in 2 h and 5 days with 1 ECG.
Tumorbiopsie: 1-2 times optional.

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

• Female and male patients >= 18 years of age.
• Stage IIIB/IV EGFR mutant NSCLC, histologically or cytologically confirmed.
• Patients with controlled brain metastases may participate in the trial. See protocol page 14 for details.
• Measurable disease.
• ECOG performance status 0, 1.
• HBV under control and HCV negative., Specific criteria groups 1-6 (see also protocol page 14-15) for phase I and II:
Group 1:
• EGFR activating mutation (e.g., L858R and/or ex19del)
• no systemic antineoplastic therapy for advanced NSCLC (no more than 1 cycle of chemotherapy in the advanced setting is allowed)

Group 2:
• EGFR activating mutation (e.g., L858R and/or ex19del) and
• acquired EGFR T790M mutation
• progressed on 1 and only 1 prior treatment with a 1st-generation EGFR TKI or 2nd-generation EGFR TKI
• no more than 3 prior lines of systemic antineoplastic therapies in the advanced setting
• EGFR TKI treatment must be the last prior treatment before study entry
Group 3:
• *de novo* EGFR T790M mutation (see protocol page 14-15)
• no more than 3 prior lines of systemic antineoplastic therapies in the advanced setting
• no prior treatment with any therapy known to inhibit EGFR
Group 4:
• EGFR exon 20 insertion or deletion
• no more than 3 prior lines of systemic antineoplastic therapies in the advanced setting
Group 5:
• EGFR activating mutation (e.g., L858R and/or ex19del) and
• without an acquired EGFR T790M mutation
• progressed on 1 and only 1 prior treatment with a 1st-generation EGFR TKI or 2nd-generation EGFR TKI
• no more than 3 prior lines of systemic antineoplastic therapiesin the advanced setting
• EGFR TKI treatment must be the last prior treatment before study entry
Group 6:
• EGFR activating mutations (e.g., L858R or ex19del) and
• an acquired T790M mutation
• had treatment with a 1st/2ndgeneration EGFR TKI
• progressed on or are intolerant to a 3rd-generation EGFR TKI
• no more than 3 prior lines of systemic antineoplastic therapies in the advanced setting
• 3rd-generation EGFR TKI treatment must be the last prior treatment before study entry

Exclusion criteria

• Interstitial pneumonitis or interstitial lung disease.
• History of malignicity last 3 year
• Strong inhibitors or inducers of CYP3A4/5 that cannot be discontinued 1 week prior to the start of EGF816.
• Pregnancy, lactation, inadequate contraception (males and females).

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-02-2017
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	EGF816
Generic name:	EGF816

Ethics review

Approved WMO Date:	23-07-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	18-11-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-01-2016
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	13-05-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-06-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-08-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-08-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-11-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-12-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	28-09-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-09-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	27-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-02-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
Other	clinicaltrilas.gov; registratienummer n.n.b.
EudraCT	EUCTR2013-004482-14-NL

Register	ID
CCMO	NL54070.031.15