A phase Ib open label clinical trial of continuous once daily oral treatment usin BIBW 2992 plus cetuximab (Erbitux) in patients with non-small cell lung cancer (NSCLC) with progression following prior erlotinib (Tarceva) or gefitinib (Iressa)

Published: 21-12-2009
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The primary aim of this study is to determine the Maximum Tolerated Dose (MTD) of BIBW2992 treatment in combination with cetuximab in patients with Non-Small Cell Lung Cancer with acquired resistance to erlotinib or gefitinib.Safety,...

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

Summary

ID

NL-OMON36313

Source
ToetsingOnline

Brief title
Continuous treatment with BIBW2992 + cetuximab in NSCLC

Condition

- Respiratory tract neoplasms

Synonym
lung cancer, non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: Boehringer Ingelheim bv

Intervention

Keyword: maximum tolerated dose, safety & pharmacokinetics, targeted, tumor response

Outcome measures

Primary outcome

The primary objective of this trial is to determine the maximum tolerated dose (MTD) and recommended Phase II doses for the combination of BIBW 2992 and cetuximab in patients with non-small cell lung cancer and acquired resistance to erlotinib or gefitinib.

Secondary outcome

1) Safety of BIBW 2992 when administered together with cetuximab as indicated by intensity and incidence of adverse events, graded according to NCI CTCAE Version 3.0 (R04-0474)

2) Pharmacokinetic parameters of BIBW 2992 and cetuximab in the applied treatment setting

3) Objective tumor response (Complete Response [CR] and Partial Response [PR]) determined by RECIST v1.1)

4) Disease control (CR, PR and Stable Disease [SD] determined by RECIST v1.1)

5) Progression-free survival (PFS)

6) Duration of disease control

7) Duration of objective response

Study description

Background summary

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death globally with an estimated one million new cases diagnosed and 880,000 deaths in the USA each year. The introduction of the EGFR-TKIs gefitinib and erlotinib has dramatically changed the clinical management of patients with advanced NSCLC. For the first time, a significant clinical benefit has been achieved by a treatment that appeared to control NSCLC progression with acceptable levels of toxic side effects through a defined and specific, targeted molecular mechanism.

Most significant response to EGFR TKI was seen in NSCLC patients with somatic EGFR (Exon 19 en Exon 21) sensitizing mutations.
However, their overall benefit has been limited by the emergence of secondary EGFR-resistance mutations. There seems to be a specific problem with patients who initially reacted positively to EGFR-TKIs.

Preclinical data have suggested that *second-generation* EGFR inhibitors may be able to overcome T790M-mediated resistance (R06-1267). BIBW 2992 is a highly potent dual EGFR and HER2 inhibitor with anti-tumor activity in both drug sensitive L858R and the
drug-resistant T790M xenograft models (P08-06904). Phase II trial in the first line (chemo-naive) and 2nd line treatment (after failure 1st chemo regiment) show good results.

Cetuximab is a chimeric human-murine monoclonal antibody that binds competitively and with high affinity to the extracellular domain of EGFR. Cetuximab has been approved by the FDA and EMEA for the treatment of colorectal and head and neck cancers.

Pre-clinical trials with a combination of the two drugs show a stronger decrease of the tumor size with Complete response.than the individual treatments. The combination results in a significant depletion of total EGFR (cetuximab) and phosphorylated EGFR (BIBW 2992).

Taken together, the currently available data support the clinical testing of irreversible inhibitors of EGFR in combination with cetuximab to prove their synergistic effect of overcoming acquired resistance to EGFR-TKI in NSCLC patient population.

Study objective

The primary aim of this study is to determine the Maximum Tolerated Dose (MTD) of BIBW2992 treatment in combination with cetuximab in patients with Non-Small Cell Lung Cancer with acquired resistance to erlotinib or gefitinib.
Safety, pharmacokinetics and anti-tumor acivity will be evaluated.

Note: pharmacokinetics is not applicable for patients enrolled after amendment 3.

Study design

Fase Ib, open label, dose escalation study

Intervention

Dose finding phase:
First cohort (1a) is BIBW 2992 40 mg /day in combination with cetuximab 250 mg/m2.
3-6 patients will be treated in one cohort depending on the number of dose limiting toxicities (DLTs) reported with one cohort.

MTD expansion cohort:
As of 19 October 2010 all new patients are treated at MTD of 40 mg BIBW 2992 and 500 mg/m2 cetuximab

As of amendment 4 all patients are treated in two arms:
1. Combination arm: combination treatment with BIBW 2992 and cetuximab at MTD
2. Sequential arm: initial treatment with monotherapy BIBW 2992 40 mg/day, followed by combination treatment with BIBW 2992 and cetuximab after progression while on BIBW 2992 at MTD

See for more details: protocol page 32-37.

Study burden and risks

Patients with advanced NSCLC who have failed at least one line of cytotoxic chemotherapy and who achieved an initial clinical benefit (at least SD for more than 6 months) from a previous treatment with erlotinib or gefitinib prior to disease progression represent a molecularly well defined patient subpopulation. The tumors of many of these patients harbor the sensitizing Exon 19 and/or Exon 21 EGFR mutations as well as acquired T790M mutation responsible for resistance to previous therapy with reversible EGFR-TKIs. For these patients there is no approved therapy and best supportive care may be considered as the standard treatment.

As a potent, irreversible EGFR-small molecule inhibitor active against the T790M EGFR mutation, BIBW 2992 in combination with cetuximab may possess the therapeutic activity to overcome this acquired resistance

Due to targeting on the same receptor, augmented skin toxicity is expected when combining BIBW 2992 with cetuximab. Skin adverse events are rarely dose- or treatment-limiting, and may diminish in intensity with continued exposure to the study drugs.
The combination therapy of cetuximab and erlotinib in a Phase I/II trial in patients with lung adenocarcinoma and acquired resistance to erlotinib reported by MSKCC (R09-1561) is well tolerated, with an acceptable dermatologic side effect profile. In this study, it is expected that
the targeted patient population can tolerate the combination regimen based on the prior substantial EGFR-TKI treatment experience.

Interstitial pneumonitis has been observed as a class effect with EGFR inhibitors including cetuximab and BIBW 2992. Patients experiencing acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever) will be immediately assessed.

Considering the lack of approved therapeutic options for patients with advanced, progressive NSCLC who have failed cytotoxic chemotherapy and who were initially sensitive to EGFR-symptoms, and maintenance or improvement of the quality of life are conceivable benefits. The anticipated benefit of the therapy of BIBW 2992 in combination with cetuximab is assumed to outweigh its risks.

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. pathologically or cytologically confirmed diagnosis of NSCLC (recurrent, stage IIIB with pleural effusion or IV)
2. Either or both of the following:
- A tumor which harbors an EGFR-mutation known to be associated with drug sensitivity (i.e. G719 X, exon 19 deletion, L858R, L861Q). A tumor which harbors exon 20 insertion or de novo T790M mutation is eligible for the treatment in the sequential arm
-Objective clinical benefit from treatment with an EGFR TKI as defined by either:
a. Documented partial or complete response (RECIST) or
b. stable disease for 6 months (or longer) as defined by RECIST in absence of radiographic progression after initiation of gefitinib or erlotinib; or stable disease/PR/CR >=12 weeks as defined by RECIST after initiation of BIBW 2992
3. Systemic progression of disease (RECIST v1.1) while on continuous treatment with erlotinib or gefitinib or BIBW 2992 within the last 30 days. Patients whose disease progresses only in the central nervous system (CNS) are not eligible.
4. No intervening systemic therapy between cessation of gefitinib or erlotinib or BIBW 2992 and initiation of the treatment in the study.
5. Adequate tumor-derived material such as fresh or archived tumor tissue or pleural fluid from malignant pleural effusion after disease progression on erlotinib/gefitinib/BIBW 2992 must be made available for EGFR mutation analysis.
see for further criteria page 26 of the protocol.

Exclusion criteria

1. Prior treatment with EGFR targeting antibodies
2. Prior severe infusion reaction to a monoclonal antibody
3. Major surgery within 28 days or minor surgery within 14 days of the start of the study treatment

4. Radiotherapy less than two weeks prior to the start of the study treatment
6. Less than three days from prior treatment with gefitinib or erlotinib.
7. Symptomatic brain metastases.
8. Other malignancies diagnosed within the past five years unless treated with curative intent. Patients with inactive malignancy may be eligible upon discussion and agreement between investigator and sponsor

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):	30-09-2010
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Erbitux
Generic name:	cetuximab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	geen
Generic name:	afatinib

Ethics review

Approved WMO

Date:	21-12-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-10-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-10-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-12-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-12-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-12-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	16-01-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-11-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2009-015911-42-NL
ClinicalTrials.gov	NCT01090011

Register	ID
CCMO	NL30193.042.09