A phase II study of gefitinib and fulvestrant in patients with advanced EGFR mutated non small cell lung cancer pretreated with reversible EGFR tyrosine kinase inhibitors

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2.1 Primary objectiveTo assess the rate of no progression (NPR) at 8 weeks following treatment with the combination of gefitinib and fulvestrant in EGFR mutated patients who failed previous treatment with reversible EGFR TKI*s (gefitinib or...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON37908

Source
ToetsingOnline

Brief title
Gefitinib and fulvestrant in EGFR mutated NSCLC

Condition

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

Synonym
advanced stage non-small cell lung cancer, metastatic non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: EGFR, Fulvestrant, Gefitinib, NSCLC

Outcome measures

Primary outcome

Primary Efficacy Endpoint

After 8 weeks of treatment start all patients that are evaluated for tumour response and are Stable Disease or better (according to RECIST criteria) will be classified as *non-progressive*. The study drug will be of interest for further study as single agent in this tumour type if at least 24/46 (52.2%) of patients are *non-progressive* within 8 weeks. (Patients without post baseline tumour assessment will be regarded as progressive in the interim and the final analysis).

Secondary outcome

Secondary Efficacy Endpoints

Quantitative and qualitative toxicities of this regimen:

Toxicities in terms of quality and quantity will be measured according to CTC AE 4.0

Duration of response for responding patients

Each subject will be assigned a best objective response. This is defined as the best response recorded from the start of treatment until disease

progression/recurrence (according to RECIST criteria). To be assigned the status of PR or CR, changes in tumour measurements must be confirmed by repeated assessments that should be performed no less than 4 weeks after the criteria for response are first met.

The Disease Control Rate is defined as the number of CR+PR+SD patients.

Objective response will be summarized in a descriptive manner.

The analysis of duration of tumour response will be based on responding patients. Duration of response is defined as the time from first response to the time of documented disease progression or death (assuming confirmation of response at least 4 weeks after initial documentation). Subjects still responding to treatment at the time of analysis will be treated as censored observations for duration of response on the date of the last tumour assessment.

Time to Progression or Death

The Time to Progression is defined as the time from start of treatment to the date of the first documented progression (according to RECIST criteria) or the date of death for any reason in the absence of PD.

Progression Free survival

PFS is defined as the time from date of randomization to date of first observed disease progression (radiological or clinical, whichever is earlier) or death due to any cause, if death occurs before progression is documented. The actual date of tumour assessments will be used for this calculation. PFS for patients

without disease progression or death at the time of analysis will be censored at the last date of tumour evaluation. PFS for patients who have no tumour assessments after baseline will be censored at day 1.

Overall Survival

Overall survival will be determined from the date of start of treatment to the date of death irrespective of the cause of death. Patients who have not died at the time of the final analysis will be censored at the date of last contact.

Study description

Background summary

In the Western world lung cancer remains the first cause of cancer related deaths in men and has surpassed that due to breast cancer in women (1). Recently it has been recognized that a subgroup of patients with non-small cell lung carcinoma (NSCLC) that harbour an activating Epidermal Growth Factor Receptor (EGFR) mutation (exon 19 deletions and L858R point mutations) are sensitive to treatment with EGFR Tyrosine Kinase Inhibitors (TKI*s). These patients comprise approximately 10-15% of all patients with adenocarcinoma of the lung. Recent phase III trials have shown that treatment with reversible EGFR TKI*s (gefitinib, erlotinib) result in an unprecedented objective response rate of approximately 70% and another 25% disease stabilization rate (2). However, invariably these patients relapse and currently no effective treatment is available. Correlative studies have shown that upon relapse several resistance mechanisms are operational. Half the patients have a secondary EGFR mutation known as the T790M mutation. It*s net result is that the affinity for currently available EGFR TKI*s is decreased markedly so that these inhibitors cannot effectively compete for ATP and signal transduction through the EGFR signaling pathway is restored resulting in tumour growth. For these patients treatment with irreversible EGFR TKI*s (afatinib) may be an option as was shown in promising early clinical trials (3-5). Results from phase III studies are soon expected (6). Approximately 10% of patients exhibit Met amplification in their tumours upon relapse. Here, clinical research is focusing on simultaneous inhibition of the EGFR and c-Met pathway. Resistance mechanisms in the remaining 40% of patients to date are unclear. In the recent years it has become apparent, at least from in vitro studies, that there is an interactive

cross-talk between the estrogen receptor pathway and the epidermal growth factor receptor pathway in NSCLC cells (7) Substantial evidence has accumulated that estrogen receptors are expressed in NSCLC. In particular, the Estrogen Receptor B (ERb) has shown to be expressed in over 50% of resected NSCLC of both men and women and is associated with adverse outcome (8-10). Lung cancer cells respond to estrogens with proliferation and it is thought that this effect is mainly mediated through the ERb pathway as it is this type of ER that is expressed abundantly in both normal and malignant lung tissue (11). Subsequent studies have shown that treatment of NSCLC cells in vitro with oestradiol results in downregulation of EGFR, whereas treatment with the antioestrogen fulvestrant increased EGFR expression (12). Modulation of the EGFR pathway effects ERb expression: treatment with epidermal growth factor reduced ERb expression whereas gefitinib, an EGFR TKI, increased it. These data suggest that the two pathways can substitute for one another when either is inhibited, whereas stimulation of one pathway shuts down the other. This reciprocal effect provides the rationale for simultaneous targeting of both pathways in lung cancer (7). Indeed, in vitro studies have shown that NSCLC cells treated by fulvestrant and gefitinib in combination were more likely to undergo apoptosis and the combination had significantly more antiproliferative effects as compared to treatment with either agent alone (7). In addition, there seems to exist a second type of ER-EGFR interaction in the nucleus that is independent of estrogen. Although estrogen may be produced locally in the lung, the former provides the rationale to test the combination of an anti-estrogen and EGFR TKI in both men and women independent of menopausal status (13).
Here, we propose to perform a phase II study of the combination of fulvestrant and gefitinib in patients with relapsed EGFR mutated NSCLC. The combination of fulvestrant 250 mg intramuscular every 28 days and gefitinib 250 mg per os daily has been shown to be safe and well-tolerated in a pilot trial conducted by ECOG including 22 relapsed unselected NSCLC patients (14). One patient discontinued treatment due to toxicity (grade 2 keratitis) and one patient with a history of heart failure and prior radiotherapy and pleural effusions developed grade 4 dyspnea. The one-year survival rate was 23% and a median survival of 33 weeks was obtained. Three patients had an objective tumour response. Intensity of nuclear staining of ERb of at least 60% was found to correlate with survival in 12 patients sampled. Recently the standard dose for fulvestrant in metastatic breast cancer, where the product has it*s only registration, changed from 250 mg monthly to 500 mg monthly plus a loading dose of 500 mg at day 14 (ref: SPC Faslodex; www.ema.europa.eu). This higher dose gives a better efficacy of the drug without adding additional toxicity (15).

Study objective

2.1 Primary objective
To assess the rate of no progression (NPR) at 8 weeks following treatment with the combination of gefitinib and fulvestrant in EGFR mutated patients who failed previous treatment with reversible EGFR TKI*s (gefitinib or erlotinib)

2.2 Secondary objective
- Quantitative and qualitative toxicities of this regimen
- Duration of response for responding patients
- Time to progression or death
- Progression free survival
- Overall survival

2.3 Additional exploratory study objectives
Correlation of RNA from trombocytes with time to progression and/or overall survival

Study design

STUDY DESIGN
3.1 Study design
This will be a single-centre, open-label Phase II study.

3.2 Statistical design
Simon*s optimal two-stage design to test if the drug combination is effective.

3.3 Procedure for registration
After verifying that the patient meets all eligibility criteria, has signed the Informed Consent Form, the investigator will request registration by sending in the registration form to the VUMC hospital, Department of Pulmonary Diseases, fax +3120-4444328. Patients will receive a registration number.

3.4 Study drugs
The doses and schedule of gefitinib will be 250 mg/day per os. For fulvestrant the dose and schedule will be 500 mg injection intramuscular on day 1, 14, 28 and every 28 days thereafter. Fulvestrant will be provided free of charge as part of the grant for this Investigator Sponsored Study by AstraZeneca.

3.5 Duration of treatment
Gefitinib and fulvestrant will be continued until unacceptable toxicity or tumour progression. In case of documented tumour progression, patient will discontinue the trial and will receive further treatment as per investigator decision. In responding patients tumour assessments will be performed after 8 weeks of therapy. In case of documented tumour progression, patient will discontinue the trial and will receive further treatment as per investigator decision.
Recruitment is expected to be completed within 2 years of the registration of the first patient. Patients will remain on treatment until disease progression, withdrawal due to toxicity or withdrawal due to patients wish. The study will be terminated after every patient had a follow up of at least 6 months. For patients with complete remission (CR), partial response (PR) and stable disease (SD), treatment will continue until progression and/or unacceptable toxicity

and/or patient withdrawal.

Intervention

Gefitinib: Patients will be treated with gefitinib 250 mg per os daily which constitutes the standard registered dose for gefitinib.
Fulvestrant: Patients will receive an intramuscular injection of 500 mg monthly plus a intramuscular loading dose of 500 mg at day 14 (that is: on day 1, day 14, day 28 and every 28 days thereafter).

Study burden and risks

Patients accrued to the study will have to visit the outpatient department at baseline and every 4 weeks thereafter. An anamnesis, physical examination, pregnancy test (if applicable), lab test, ECG, tumour biopsy and CT-scan will be done at baseline. Anamnesis, physical examination and lab tests will be done every 4 weeks when patients visit the outpatient department. Every 8 weeks a CT-scan will be performed. On day 1, 14, 28 and monthly thereafter patients will receive a fulvestrant injection.
Besides pregnancy test (if applicable) and fulvestrant administration, the number of visits and procedures are not different from routine clinical practice.

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.Histologically or cytologically confirmed NSCLC locally advanced and metastatic disease stage IIIB and IV, that have an activating EGFR mutation, progressive on treatment with gefitinib or erlotinib. Patients with unknown mutation status that have exhibited a response to these agents or stable disease for at least 6 months while on treatment with gefitinib or erlotinib are also eligible
2. At least one unidimensionally measurable lesion meeting RECIST criteria
3. ECOG PS 0-2
4. Age > 18 years
5. Adequate organ function, including:
a. Adequate bone marrow reserve: ANC > 1.5 x 109/L, platelets > 100 x 109/L.
b. Hepatic: bilirubin <1.5 x ULN, AP, ALT, AST < 3.0 x ULN
AP, ALT, and AST <5 xULN is acceptable if the liver has tumour involvement
c. Renal: calculated creatinine clearance > 45 ml/min based on the Cockroft and Gault formula.
6. Signed informed consent
7. Male and female patients with reproductive potential must use an approved contraceptive method, if appropriate. Female patients with childbearing potential must have a negative serum pregnancy test within 14 days prior to study enrollment.
8. Estimated life expectancy >12 weeks
9. Patient compliance and geographical proximity that allow adequate follow up.
10. NSCLC with an activating sensitising EGFR TK mutation as determined by using a well-validated and robust methodology.

Exclusion criteria

1. Pregnant or lactating women
2. Patients who are poor medical risks because of non-malignant disease as well as those with active uncontrolled infection.
3. Documented brain metastases unless the patient has completed local therapy for central nervous system metastases and has been off corticosteroids for at least two weeks before enrollment.

4. Concomitant treatment with any other experimental drug under investigation.
5. Known severe hypersensitivity to gefitinib or any of the excipients of the product.
6. Presence of EGFR TK mutation reported to confer resistance to EGFR TKI: i.e., exon 20 point mutation (T790M or S768I EGFR) or exon 20 insertion as determined by using a well-validated and robust methodology.
7. Past medical history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active interstitial lung disease.
8. Concomitant use of known CYP 3A4 inducers such as phenytoin, carbamazepine, rifampicin, barbiturates, or St John's Wort.
9. Previous enrolment or treatment in the present study.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	48
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	faslodex
Generic name:	fulvestrant
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Iressa
Generic name:	gefitinib

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-03-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2012
Application type:	First submission
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

ID: 28300
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2012-000345-12-NL
CCMO	NL39476.029.12
OMON	NL-OMON28300