Gefitinib and fulvestrant in patients with advanced, EGFR mutated NSCLC pretreated with EGFR TKI's.

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Patients with advanced, EGFR mutated NSCLC pretreated with reversible EGFR TKI's will be treated with gefitinib and fulvestrant. The response rates after 8 weeks will be evaluated.

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON28300

Bron
Nationaal Trial Register

Verkorte titel
GE study

Aandoening

Patients with pathologically documented NSCLC with an EGFR mutation, who failed previous treatment with reversible EGFR TKI’s (gefitinib or erlotinib).

Ondersteuning

Primaire sponsor: VU University Medical Center
Overige ondersteuning: VU University Medical Center

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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).

Toelichting onderzoek

Achtergrond van het onderzoek

Background of the study:

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. 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. 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. 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. 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. 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.

Here, we propose to perform a phase II study of the combination of fulvestrant and gefitinib in patients with relapsed EGFR mutated NSCLC. 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. This higher dose gives a better efficacy of the drug without adding additional toxicity.

Objective of the study:

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).

Secondary objective:

1. Quantitative and qualitative toxicities of this regimen;

2. Duration of response for responding patients;

3. Time to progression or death;

4. Progression free survival;

5. Overall survival.

Additional exploratory study objectives:

Correlation of RNA from trombocytes with time to progression and/or overall survival.

Study design:

This will be a single-centre, open-label Phase II study.

Statistical design:

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

Study drugs/ intervention:

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.

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.

Study population:

Patients with pathologically documented NSCLC with an EGFR mutation, who failed previous treatment with reversible EGFR TKI’s (gefitinib or erlotinib).

Doel van het onderzoek

Patients with advanced, EGFR mutated NSCLC pretreated with reversible EGFR TKI's will be treated with gefitinib and fulvestrant. The response rates after 8 weeks will be evaluated.

Onderzoeksopzet

Before treatment initiation:

1. Informed consent;

2. Demographics, medical history, adverse events and concomitant medications;

3. Pregnancy test;

4. Physical examination, performance status, vital signs;

5. Height and weight;

6. Complete blood count;

7. Blood chemistry;

8. ECG;

9. Blood sample for RNA analysis;

10. Disease assessment;

11. CT-scan (optional: MRI-scan or PET-scan);

12. Tumour biopsy:

A. Lesion is selected based upon a trade of between the lowest complication risk and the highest success rate);

B. ERβ expression and EGFR status will be analyzed.

At day 1 of treatment:

Injection of fulvestrant at the outpatient department.

At day 14 of treatment:

Injection of loading dose of fulvestrant.

Every visit (4-weekly):

1. Check intake of gefitinib and concomitant medication;

2. CTC-AE 4.0;

3. Clinical examination (blood pressure, heart rate, WHO performance, weight);

4. Standard lab tests (same as baseline);

5. Blood sample for RNA-analysis from trombocytes.

Every 8 weeks:

CT thorax.

At disease progression:

1. Blood sample for RNA-analysis from trombocytes;

2. Tumour biopsy for translational research.

Onderzoeksproduct en/of interventie

Daily gefitinib 250 mg per os and monthly fulvestrant 500 mg intramuscular plus a loading dose of 500 mg fulvestrant intramuscular on day 14. This will be given until progression.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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 1.1 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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-05-2012
Aantal proefpersonen:	48
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	19-03-2012
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 37908
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL3212
NTR-old	NTR3362
CCMO	NL39476.029.12
ISRCTN	ISRCTN wordt niet meer aangevraagd.
OMON	NL-OMON37908

Resultaten

Samenvatting resultaten
N/A