# Neurocognitieve effecten van lorlatinib: hoe de zorg te verbeteren

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Patients that are treated with lorlatinib will have an impairment in speech, mood and several cognitive domains. With extensive testing, more impairments will be found than with CTCAE criteria alone.

| | |
|---|---|
| **Ethische beoordeling** | Positief advies |
| **Status** | Werving nog niet gestart |
| **Type aandoening** | - |
| **Onderzoekstype** | Observationeel onderzoek, zonder invasieve metingen |

## Samenvatting

### ID

NL-OMON27508

**Bron**
Nationaal Trial Register

**Verkorte titel**
lorlatinib neurocognitief

**Aandoening**

NSCLC; lorlatinib; ALK; ROS1; neurocognitive adverse events

### Ondersteuning

**Primaire sponsor:** academisch ziekenhuis maastricht
**Overige ondersteuning:** Dirkje Postma Award
others to be confirmed yet

### Onderzoeksproduct en/of interventie

### Uitkomstmaten

**Primaire uitkomstmaten**

- change for every neurocognitive endpoint during treatment with lorlatinib compared to

baseline

# Toelichting onderzoek

### Achtergrond van het onderzoek

Lorlatinib is a selective, potent, brain-penetrant nextgeneration ALK and ROS1 TKI for NSCLC. Lorlatinib achieves high response rates with durable control in the brain. The most common adverse events (>30%) with the standard dose
are hypercholesterolemia, hypertriglyceridemia, peripheral oedema, and peripheral neuropathy. Other common adverse events are neurocognitive disturbances. These neurological
adverse events can be subdivided into cognitive, speech and mood effects. In a phase I trial Common Terminology Criteria for Adverse Events (CTCAE) grade 1-2 cognitive effects were described in 22%, 2% had grade 3 cognitive effects. Speech effects were described for 19%, all grade 1-2. In an ongoing phase II trial N=275), 64 (23.3%)had cognitive effects, of which 1.1% were grade 3, the others 1-2. 44 (16%) had mood effects, of which 1.1% were grade 3. Of the 9 patients (3.3%)
that permanently discontinued lorlatinib, 4 discontinued because of neurocognitive and/or mood effects. Dose interruptions and dose reductions occurred in respectively 4.7%) and 4.4% patients because of cognitive effects and in
respectively 8 (2.9%) and 10 (3.6%) because of mood effects. Although usually CTCAE low grade (grade 1-2), these neurocognitive effects can be discomforting and confusing for patients and their relatives and neurocognitive deficits
are well known to have a detrimental effect on quality of life. Up till now, these neurocognitive effects have only been described by CTCAE criteria for which no extensive neurocognitive testing is required to determine the exact
underlying neurocognitive impairment.

Primary objective

Evaluate for each patient the change for each neurocognitive test during treatment with lorlatinib compared to baseline.

With these results, our aim is to develop a tool which can help patients and relatives to cope with these complaints.

Secondary objectives

- Describe for all patients the neurocognitive domains (according to the neurocognitive tests) that are affected during lorlatinib treatment

- Correlate the results of the neurocognitive tests to the selfreported neurocognitive decline

- Correlate the results of the neurocognitive tests to the Common Terminology Criteria for Adverse Events (CTCAE) grading (version 5.0).

## Doel van het onderzoek

Patients that are treated with lorlatinib will have an impairment in speech, mood and several cognitive domains. With extensive testing, more impairments will be found than with CTCAE criteria alone.

## Onderzoeksopzet

All the tests will be performed at baseline (i.e. maximum one week before start of lorlatinib), after 2 weeks (+/- 3 days) of lorlatinib use and after 2 months (+/- 1 week) of lorlatinib use.

## Onderzoeksproduct en/of interventie

Neurocognitive adverse events will be evaluated by standardized neurocognitive tests that cover the most important domains of neurocognition. All the tests will be performed at baseline (i.e. maximum one week before start of lorlatinib), after 2 weeks (+/- 3 days) of lorlatinib use and after 2 months (+/- 1 week) of lorlatinib use. Testing and questionnaires will be performed by trained nurses.

The tests are not emotionally disturbing. All tests will be coded, so no patient names will be used. Instead of ¡®name¡¯, patient number will be used. The tests battery that will be used is recommended by the EORTC (16). In addition, a depression and anxiety test (HADS), a coping test and a subjective cognitive failure test (CFQ) will be performed. Adverse events will also be categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Tests are summarized below.

- Trail Making Test A. The domain measured is visual scanning speed and the outcome is measured in number of seconds to complete (0-300). Duration about 10 minutes.

- Trail Making Test B. The domain measured is divided attention and the outcome is measured in number of seconds to complete (0-300). Duration about 10 minutes.

- Controlled Oral Word Association. The domain measured is verbal fluency and the outcome is measured by an age and sex-related raw score (range 0-no upper limit). Duration 5-10 minutes.

- Hopkins Verbal Learning test revised (part A free recall, B delayed recall, C delayed recognition). The domain measured is verbal memory and the outcome is measured by immediate memory of word list rehearsed three times (maximum score = 36). After 20-30 min delay, number of words correctly recalled (maximum score = 12). Recognition is number of words recognized form a longer list (maximum score = 12). Duration 5-10 minutes with 20

minutes delay. TMT-A en B, Digit Symbol subtest en Pegboard can be performed in the waiting time to the delayed recall / recognition as they are not verbal or memory tasks.

- Digit Symbol Subtest of the WAIS III. The Domain measured is psychomotor speed and the outcome is measured by an age ¨Ccorrected subtest score (0-20). Duration about 5 minutes.

- Grooved pegboard test. The domain measured is fine motor control for dominant and non-dominant hands and the outcome is measured by number of seconds to complete (0-300). Duration about 5 minutes.

- The Hospital Anxiety and Depression scale (HADS) is a 14-item scale to assess the presence of anxiety and depressive symptoms (Zigmond & Snaith, 1983, Acta Psychiatrica Scaninavica) and takes approximately 5 minutes to fill in.

- The Cognitive Failure Questionnaire (CFQ) is a questionnaire for subjective cognitive functioning consisting of 25 questions regarding the frequency of everyday cognitive errors (Ponds et al 2006). Time to fill in 10-15 minutes.

- The Subjective Cognitive Functioning (SCF) questionnaire is a 4-item questionnaire used to assess a subjective change in 4 domains (e.g. memory, concentration, mental strain and vitality. It can be filled in within 5 minutes.

- Passive and active coping will be assessed by means of the passive reaction pattern subscale and the active problem solving subscale of the Utrecht Coping List (UCL). These subscales each consist of 7 items that are scored on a 4-point scale ranging from ¡°seldom¡± to ¡°very often¡±. (Schreurs et al 1993). It can be filled in in 5 minutes.

# Contactpersonen

## Publiek

Dept of Pulmonary Diseases, MUMC+
PO Box 5800
L. Hendriks
Maastricht 6202 AZ
The Netherlands
+31 (0) 43 387 6543

## Wetenschappelijk

Dept of Pulmonary Diseases, MUMC+
PO Box 5800
L. Hendriks
Maastricht 6202 AZ

The Netherlands
+31 (0) 43 387 6543

# Deelname eisen

## Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- Stage IV NSCLC with ALK or ROS1 rearrangement, indication in daily clinical care to start lorlatinib treatment

- Age ≥ 18 years

- Ability to understand neurocognitive testing

- Written informed consent

## Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Neurodegenerative diseases (such as Alzheimers disease)

- Psychiatric disease

- Symptomatic brain metastases / neurological symptoms due to previous cranial irradiation (e.g. due to radiation necrosis)

- Inability to understand the testing / questionnaires

# Onderzoeksopzet

## Opzet

| | |
|---|---|
| Type: | Observationeel onderzoek, zonder invasieve metingen |
| Onderzoeksmodel: | Anders |
| Toewijzing: | N.v.t. / één studie arm |
| Blindering: | Open / niet geblindeerd |

| | |
|---|---|
| Controle: | N.v.t. / onbekend |

### Deelname

Nederland

| | |
|---|---|
| Status: | Werving nog niet gestart |
| (Verwachte) startdatum: | 01-11-2018 |
| Aantal proefpersonen: | 20 |
| Type: | Verwachte startdatum |

## Ethische beoordeling

Positief advies

| | |
|---|---|
| Datum: | 17-10-2018 |
| Soort: | Eerste indiening |

## Registraties

### Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

### Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

### In overige registers

| Register | ID |
|---|---|
| NTR-new | NL7357 |
| NTR-old | NTR7565 |
| Ander register | : METC azm/UM 2018-0719 |

## Resultaten