Standard dose alectinib versus Therapeutic Drug Monitoring guided alectinib dosing

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In lung cancer patients treatment with EGFR-TKI has been shown to be influenced by e.g. body weight and renal impairment. Adapting the EGFR-TKI dose could help in preventing major side effects and improve outcome of the treatment4. For ALK-TKI this...

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON24311

Bron
NTR

Verkorte titel
Adapt Alec Trial

Aandoening

ALK fusion in stage IV NSCLC

Ondersteuning

Primaire sponsor: University Medical Center Groningen
Overige ondersteuning: UMCG

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

The primary endpoint is a a prolonged mPFS in the TDM-guided dosing arm for the subgroup who had a Cmin < 435 ng/mL at a certain time point during treatment, compared to these patients in the fixed dosing arm

Toelichting onderzoek

Achtergrond van het onderzoek

Currently, over 40% of all recently approved oncolytics are oral agents.1 Compared with the more traditional intravenous therapies, these oral agents are less invasive and more patient friendly. On the other hand, due to home administration, patient's adherence could be compromised.2 Secondly, the oral administration route makes these agents more prone to drug-drug and drug-food interactions, both resulting in suboptimal drug exposure, with rates varying between only 30% and 70% of desired drug exposure targets.3 Notably, overdosing causes unnecessary and preventable side effects, while underdosing results in reduced effects and tumour growth.
In lung cancer patients treatment with EGFR-TKI has been shown to be influenced by e.g. body weight and renal impairment. Adapting the EGFR-TKI dose could help in preventing major side effects and improve outcome of the treatment4. For ALK-TKI this has not been studied largely yet.
Despite the relative short treatment period of on average a year, and the severity of the disease, still 20% of lung cancer patients have suboptimal adherence.5 This may partly help to explain why survival of patients with metastatic non-small cell lung carcinoma (NSCLC) in real-world daily practice is nearly one quarter shorter than for patients included in clinical trials.6 Adherence is the single most modifiable risk factor that comprises treatment outcomes but is difficult to measure and no studies so far have employed objective methods. Objective, long-term adherence data can support patients' self-management in the outpatient setting, allows enhanced physician clinical decision making and informs therapeutic drug monitoring (TDM) targets (dose increase or decrease).
Alectinib is used in first and second line settings in ALK positive advanced lung cancer as standard of care.7 Groenland et al. found in an exposure-response analysis of alectinib a median alectinib Cmin of 517 ng/mL (range: 141-1944 ng/mL), with an interindividual variability of 57%. In total, 37% of the patients had a median Cmin< 435 ng/mL. The median PFS was 12.8 months vs. not estimated (95%CI: 19.8 months – not estimated) for patients with Cmin below or above 435 ng/mL, respectively (p=0.04, log-rank) (Figure 1). Multivariable analysis corrected for WHO performance status and prior treatment with ALK-inhibitor(s) resulted in hazard ratio of 4.29 (95%CI: 1.33-13.90, p=0.015) in favour of patients with higher drug exposure.8
Therefore, patients should have an alectinib Cmin ≥ 435 ng/mL, which could be established by therapeutic drug monitoring (i.e. adjusting the dose based on measured drug concentrations). Taken together, we hypothesize that the PFS will increase by more than 10 months comparing therapeutic drug monitoring (TDM) and increasing the dose of alectinib if the Cmin threshold of 435 ng/mL is not reached and with fixed alectinib dosing.

Doel van het onderzoek

In lung cancer patients treatment with EGFR-TKI has been shown to be influenced by e.g. body weight and renal impairment. Adapting the EGFR-TKI dose could help in preventing major side effects and improve outcome of the treatment4. For ALK-TKI this has not been studied largely yet.

Onderzoeksopzet

at regular visits (4,8 and every 8 weeks thereafter)

Onderzoeksproduct en/of interventie

ECG, bloodsampling, scans, optional biopsy

Contactpersonen

Publiek

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Patients with locally advanced or metastatic NSCLC (stage IIIB to stage IV by AJCC 8th)

2. Male or female ≥18 years old

3. ECOG Performance Status of 0−2

4. Histologically or cytology confirmed NSCLC

5. Documented ALK rearrangement based on an EMA approved test

6. Patients can either be chemotherapy-naïve or have received one line of platinum-based chemotherapy

7. Patients with brain or leptomeningeal metastases are allowed on study if the lesions are asymptomatic without neurological signs and clinically stable for at least 2 weeks without steroid treatment. Patients who do not meet these criteria are not eligible for the study. However, they can be re-screened after completing WBRT or gamma –knife treatment. They must have completed any corticosteroid therapy ≥2 weeks prior to the first dose of study treatment.

8. Measurable disease (by RECIST criteria version 1.1) prior to the first dose of study treatment

9. Signed written Institutional Review Board (IRB)/Ethical Committee (EC) approved informed consent form, prior to performing any study-related procedures.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Any significant concomitant disease determined by the investigator to be potentially aggravated by the investigational drug

2. Consumption of agents which modulate CYP3A4 or agents with potential QT prolonging effects within 14 days prior to admission and during the study (see concomitant medication restrictions)

3. Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study, or absorption of oral medications, or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the subject in this study.

4. Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures; those conditions should be discussed with the patient before trial entry.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	Geneesmiddel

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	23-03-2022
Aantal proefpersonen:	196
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Toelichting
undicided

Ethische beoordeling

Positief advies

Datum:	26-04-2021
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	NL9441
Ander register	METc UMCG : METc 202000251

Resultaten

Samenvatting resultaten
NA