Standard dose alectinib versus Therapeutic Drug Monitoring guided alectinib dosing

Published: 02-02-2022
Last updated: 14-09-2024

This study has been transitioned to CTIS with ID 2023-506886-76-00 check the CTIS register for the current data. The primary objective will be a prolonged mPFS for the TDM-guided dosing cohort versus the standard fixed dosing cohort in the group of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52135

Source
ToetsingOnline

Brief title
Adapt Alec Trial

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Non-small cell lung cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Alectinib, ALK fusion, Non-small cell lung cancer, Therapeutic drug monitoring

Outcome measures

Primary outcome

The main endpoint will an increase in progression free survival (PFS according to RECIST v1.1) in the subgroups of patients with an alectinib Cmin treshhold <435 ng/mL in the TDM-guided dosing cohort versus the same subgroup in the fixed dosing cohort

Secondary outcome

The secondary objectives are:

1. Feasibility and safety of TDM. This will be measured as percentage of successful TDM measures, in which successful is defined as target attainment with manageable toxicity.

2. Physician adherence to TDM advice. This will be measured as the percentage of dose recommendations that are implemented by the treating physicians.

3. Overall response rates (ORR). ORR will be defined as partial response or complete response (according to RECIST v1.1) percentage of the total treated population.

4. Median overall survival (mOS). OS will be defined as the time from randomization to death from any cause in the total population. Patients who do not die or are lost to follow-up will be censored at their last available date.

5. Intracranial PFS. The intracranial PFS will be measured as time from start of treatment to progressive disease in the brain, or death from any cause. Patients who did not die or progress, or lost to follow-up, will be censored at

their last available date.

6. Patient adherence. This will be estimated by pill counts of returned medication as well as a patient diary on drug intake.

7. Toxicity related to the plasma concentration and dose increases. This will be defined as AE*s in the subgroups with Cmin < 435 ng/mL and all Cmin >= 435 ng/mL, and in patients who did and who did not receive a PK-guided dose increase.

8. Quality of life (QoL). This will be determined using the EORTC QLQ_LC13 as addition to the QLQ-C30 questionnaire, and the EQ-5D-5L questionnaire.

9. Cost-effectiveness. This will be determined by the incremental cost-effectiveness ratio based on costs and quality adjusted life-years (QALYs)

10. Alectinib-M4 concentrations. These will be measured in the alectinib plasma samples.

Study description

Background summary

Currently, over 40% of all recently approved oncolytics are oral agents. 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. 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 treatment. 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. 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. 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

Study objective

This study has been transitioned to CTIS with ID 2023-506886-76-00 check the CTIS register for the current data.

The primary objective will be a prolonged mPFS for the TDM-guided dosing cohort versus the standard fixed dosing cohort in the group of patients with an alectinib Cmin below the threshold of< 435 ng/mL.
The secondary objectives are functioning and safety of TDM, overall response rates (ORR), median overall survival (mOS), intracranial PFS, physician adherence and toxicity (also in relationship to alectinib plasma concentrations and dose increases), quality of life, cost-effectiveness en alectinib M4-concentrations.

Study design

A phase IV randomized controlled trial between TDM guided dosing (Arm A) and standard dose (Arm B) alectinib will be conducted

Intervention

One group (Arm A) will receive standard dose alectinib (600mg BID) and the other group will receive alectinib adapted based on TDM (Arm B; dose adaptations based on drug exposure in case of limited toxicity)

Study burden and risks

In both treatment groups, plasma samples will be drawn at different time points (every 8 weeks during the first year of treatment and every 8 weeks from the second year of treatment onwards). This blood draw is in combination with standard blood draws for monitoring organ function (eg liver and renal tests). For the intervention group, TDM results will be available directly (within 1-2 weeks) and used to adapt the alectinib dose. We expect that this intervention will result in prolonged mPFS. For the fixed dosing group, the samples will be analysed at the end of the study.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

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*4

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

Exclusion criteria

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.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-03-2022
Enrollment:	186
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alecensa
Generic name:	Alectinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-02-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-03-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-11-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-04-2023
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
EU-CTR	CTIS2023-506886-76-00
EudraCT	EUCTR2020-001737-NL
CCMO	NL77596.042.21
Other	NL9441