Combining Afatinib and Concurrent Chemotherapy, Followed by Osimertinib and Concurrent Chemotherapy, in Untreated EGFR Positive NSCLC Tumors

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON28617

Source
Nationaal Trial Register

Brief title
COMBINATION

Health condition

Non small cell lung cancer

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: The translational research part is supported by Boehringer Ingelheim

Intervention

Outcome measures

Primary outcome

Disease control rate (DCR) at 18 months, defined as the rate of patients that are still on treatment using either afatinib or osimertinib without radiological disease progression according to RECIST (v1.1). If patients develop oligo-progressive disease that is amenable to local treatments such as stereotactic radiotherapy and if the patient has clinical benefit of the ongoing TKI treatment, the treating physician may (in the best interest of the patient) treat the oligo-progressive site(s) locally and continue the TKI (in part-1 and part-2) beyond progression, as per current standard of care guidelines. The efficacy of this sequential approach will be compared to the front-line osimertinib outcome data, as reported by the FLAURA trial.

Secondary outcome

1. Progression Free Survival (PFS) as determined using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and defined as time from initiation of afatinib to the development of new lesions, progression of existing lesions, or death, whichever comes first
2. Overall Survival (OS). Time frame: initiation of afatinib until death.
3. Objective response rate at 6 and 12 weeks according to RECIST v1.1 after start of afatinib
4. Objective response rate at 6 and 12 weeks according to RECIST v1.1 after start of osimertinib
5. Safety of afatinib and osimertinib intercalated with 2 cycles of carboplatin-pemetrexed.
Exploratory endpoints
1. The baseline tumor biopsy (and all archival biopsies) and additional blood samples (before start of afatinib, at defined timepoints during treatment and upon progression) will be used for assessing the time to disappearance and time to re-appearance of the EGFR mutation in ctDNA both after start of afatinib and osimertinib.

Study description

Background summary

Osimertinib monotherapy is now the preferred treatment option in EGFR mutation positive non-small cell lung cancer (NSCLC). However, a sequential combination strategy using first line afatinib in with a short course of chemotherapy, followed by osimertinib with a short course of chemotherapy (in T790M positive tumors) could increase the targeted therapy efficacy option for these patients.
Study design: this is a single arm, open label, multicenter phase II study. A total of 21 evaluable patients are needed.
Study population: TKI-naïve advanced EGFRm+ del19/L858R NSCLC patients who are eligible for treatment with EGFR TKI and chemotherapy. Patients with CNS metastases will be excluded.

Study objective

We hypothesized that treating advanced stage EGFR mutation positive NSCLC in first line

with afatinib and osimertinib in second line (in T790M positive tumors) will cause an apoptotic cell death in a large part of TKI-sensitive cancer cells, resulting in a large reduction of the tumor bulk. Adding cytotoxic chemotherapy after 6 weeks of EGFR-TKI will destroy remaining TKI-resistant subclones at an early stage, when the TKI-resistance tumor volume is the smallest and most vulnerable. We will administer only 2 cycles of chemotherapy to limit toxicity, while maintaining a substantial anti-cancer effect. After progression on afatinib-chemotherapy combination, the majority of patients will develop T790M and will be able treated by osimertinib-chemotherapy combination.
So, this strategy will allow us to timely sequence the most appropriate drugs (afatinib and osimertinib with chemotherapy) to get the highest anti-cancer efficiency. In this way, we will avoid long periods of maintenance treatments with chemotherapy or anti-VEGFR treatments that are associated with toxicity, costs, and necessitate the patients to come into the ward for intravenous medication. The limited cycles of chemotherapy also allows
the treating physician to again treat the patient with the same chemotherapy regimen once progression occurs after all sensible targeted therapy options have been used.
Therefore, we hypothesize that this sequential combination strategy will be more effective than other available strategies and will improve the quality of patient care as compared to current general practice.

Study design

The primary endpoint will be evaluated at 18 months of inclusion using RECIST1.1. The secondary and explorary endpoints will be evaluated using RECIST1.1 every six weeks, survival data, molecular analysis of histologic specimen at baseline and upon progression, and blood samples dd-PCR every six weeks initially and upon progression.

Intervention

This study consists of 2 parts. Part 1 is defined as a first line treatment with afatinib orally (30 mg once a day) for the first 6 weeks, followed by concurrent use of afatinib (20mg once a day, part 1B) plus 2 cycles of carboplatin and pemetrexed (21 days per cycle); followed by afatinib monotherapy (30mg once a day). Part 2 comprises a 2nd line treatment with osimertinib (80 mg once daily) after failure of part 1, only in T790M positive patients for the first 6 weeks, followed by concurrent use of osimertinib (80mg once a day) plus 2 cycles of carboplatin and pemetrexed (21 days per cycle); followed by osimertinib monotherapy (80mg once a day).

Contacts

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Eligibility criteria

Inclusion criteria

1. Histologically confirmed NSCLC, positive for EGFR exon 19 deletion or EGFR exon 21 L858R
2. WHO PS 0-2
3. Be willing and able to provide written informed consent for the trial.
4. Be above 18 years of age on day of signing informed consent.
5. Patients must have radiological measurable disease
6. Demonstrate adequate organ function, as deemed acceptable by the treating physician in the context of metastatic NSCLC:
a. Leukocytes ≥ 3,000/mm3
b. Absolute neutrophil count (ANC) ≥ 1500/mm3
c. Platelet count ≥ 100,000/mm3
d. Hemoglobin ≥ 6 mmol/L
e. Creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥40 mL/min (if using the Cockcroft-Gault formula below):
i. Female CrCl = [(140 - age) x weight x 0.85]/(0.85 x creat in mmol/L)
ii. Male CrCl = [(140 - age) x weight x 1.00]/(0.81 x creat in mmol/L)
f. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome)
g. AST and ALT ≤ 3 times the upper limit of normal

Exclusion criteria

1. Inability to provide informed consent
2. Inability to take study medications
3. Patients with CNS metastases
4. Prior EGFR TKI or platinum-doublet therapy for advanced stage NSCLC. Prior (neo)adjuvant treatments are allowed when the last administration is one year or more.
5. Evidence of interstitial lung disease or active, non-infectious pneumonitis.
6. Active infection requiring systemic therapy.
7. Active Hepatitis B or C.
8. Psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
9. Patient is pregnant or breastfeeding, or expecting to conceive within the projected duration of the trial, starting with the screening visit.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-10-2020
Enrollment:	21
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	15-10-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 52389
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL8985
CCMO	NL74383.029.20
OMON	NL-OMON52389

Study results