Safety of TKI concurrent with cranial radiotherapy in NSCLC patients; the SATIN platform trial

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Primary Objectives: - To assess whether there is an increase in acute severe toxicity (per TKI cohort) 2 weeks after completion of cranial radiotherapy measured with CTCAE v 4.0. - To assess whether there is an increase in neurotoxicity (measured...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Breast neoplasms benign (incl nipple)
Study type	Observational invasive

Summary

ID

NL-OMON54721

Source
ToetsingOnline

Brief title
SATIN

Condition

- Breast neoplasms benign (incl nipple)

Synonym
non-small cell lung cancer brain metastases

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Astra Zeneca,industrie (grants gevraagd),Roche,Takeda

Intervention

Keyword: brain metastases, cranial radiotherapy, non-small cell lung cancer, tyrosine kinase inhibitor

Outcome measures

Primary outcome

Primary Objectives:

- To assess whether there is an increase in acute severe toxicity (per TKI cohort) 2 weeks after completion of cranial radiotherapy measured with CTCAE v 4.0.

- To assess whether there is an increase in neurotoxicity (measured with neurocognitive testing, per TKI cohort) 4 months after completion of cranial radiotherapy compared to the baseline measurement.

Secondary outcome

Secondary Objectives:

- To assess whether there is an increase in neurotoxicity (per TKI cohort) 6 months after completion of cranial radiotherapy in relation to the baseline measurement.

- To assess whether there is an increase in incidence of severe toxicity (per TKI cohort) 4 months after completion of cranial radiotherapy, measured with CTCAE v 4.0, compared to baseline data.

- To assess whether there is an increase in incidence of severe toxicity (per TKI cohort) 6 months after completion of cranial radiotherapy, measured with CTCAE v. 4.0, compared to baseline data.

Exploratory:

- To assess what the intracranial PFS is per TKI cohort at 4 and at 6 months after completion of cranial radiotherapy.

- To assess what the cerebrospinal fluid penetration potential is, measured by the unbound cerebrospinal fluid-to-plasma ratio (Kp,uu), before and 2 weeks after cranial radiotherapy and to correlate this ratio with toxicity (CTCAE v 4.0) 2 weeks after cranial radiotherapy, evaluated separately for each TKI cohort

- To assess the plasma concentration of the TKI before and 2 weeks after cranial radiotherapy and to correlate this concentration with Kp,uu and toxicity (CTCAE v 4.0) 2 weeks after cranial radiotherapy (if there is also consent for liquor sampling), evaluated separately for each TKI cohort

Study description

Background summary

Non-small cell lung cancer (NSCLC) is one of the major causes of cancer related mortality worldwide.
Increasingly, new molecular features of NSCLC are being discovered, leading to an unprecedented growth of targeted agents, such as tyrosine kinase inhibitors (TKIs). Currently, TKIs are approved for metastasized NSCLC patients with a driver mutation (EGFR, ALK, ROS1). Approximately 20-35% of these patients are diagnosed with brain metastasis at initial diagnosis and are often amenable for initial treatment with a TKI. A relatively high percentage will also develop new brain metastases or progression of brain metastases during the course of their disease, often while on TKI treatment.
In patients with brain metastases both whole brain radiotherapy (WBRT) and stereotactic radiosurgery/stereotactic radiotherapy (SRS/SRT) can be considered as a local therapy. Neurotoxicity after brain radiotherapy is especially seen with WBRT, but also SRT. The radio-induced neurocognitive impairment evolves in a biphasic pattern: a subacute transient decline with a peak at four months, and a late delayed irreversible impairment several months or years after

completion of WBRT. However, these results were obtained in unselected patients with often a poor overall prognosis, and it is not clear whether the deterioration resulted from radiotoxicity or intracranial progression.
Moreover, the brain metastases itself can cause neurological complaints, also before initiation of radiotherapy. Patients with a driver mutation have a superior prognosis compared to those without, even in the presence of brain metastases. It has also been suggested that EGFR-mutated and ALK-translocated NSCLC cells have a higher radiosensitivity than wildtype NSCLC but it is unclear what the impact is on neurotoxicity after cranial radiotherapy.
In current guidelines, no advice regarding TKI use during cranial radiotherapy is given. As the TKI may still be active on extra-cranial sites, clinicians are faced with the question whether to continue the TKI or not. Especially because rapid flare of the disease is a known phenomenon after interruption of a TKI. Preclinical studies suggest that TKIs enhance radiation effects but the effects on normal tissues are unclear.
In daily practice TKI*s are given concurrent with cranial radiotherapy or they are discontinued during cranial radiotherapy because of (neuro)toxicity concerns, depending on the treating physician. When the TKI*s are being discontinued, they are stopped for approximately one week before, during and one week after the radiotherapy (i.e. approximately 3 weeks) with the risk of a systemic disease flare-up.
Advantages of combining TKI with cranial radiotherapy would be a possible synergistic effect on the brain metastases and the prevention of a systemic disease flare-up.
As cranial radiotherapy will be indicated for a significant number of these patients we want to extensively evaluate neurotoxicity in patients with a driver mutation, treated with concurrent brain radiotherapy and a TKI. Even though this concurrent treatment is rapidly becoming standard practice, detailed neurotoxicity data are not available for this patient group.

Study objective

Primary Objectives:
- To assess whether there is an increase in acute severe toxicity (per TKI cohort) 2 weeks after completion of cranial radiotherapy measured with CTCAE v 4.0.
- To assess whether there is an increase in neurotoxicity (measured with neurocognitive testing, per TKI cohort) 4 months after completion of cranial radiotherapy compared to the baseline measurement.

Secondary Objectives:
- To assess whether there is an increase in neurotoxicity (per TKI cohort) 6 months after completion of cranial radiotherapy in relation to the baseline measurement.
- To assess whether there is an increase in incidence of severe toxicity (per TKI cohort) 4 months after completion of cranial radiotherapy, measured with CTCAE v 4.0, compared to baseline data.

- To assess whether there is an increase in incidence of severe toxicity (per TKI cohort) 6 months after completion of cranial radiotherapy, measured with CTCAE v. 4.0, compared to baseline data.

Exploratory:
- To assess what the intracranial PFS is per TKI cohort at 4 and at 6 months after completion of cranial radiotherapy.
- To assess what the cerebrospinal fluid penetration potential is, measured by the unbound cerebrospinal fluid-to-plasma ratio (Kp,uu), before and 2 weeks after cranial radiotherapy and to correlate this ratio with toxicity (CTCAE v 4.0) 2 weeks after cranial radiotherapy, evaluated separately for each TKI cohort
- To assess the plasma concentration of the TKI before and 2 weeks after cranial radiotherapy and to correlate this concentration with Kp,uu and toxicity (CTCAE v 4.0) 2 weeks after cranial radiotherapy (if there is also consent for liquor sampling), evaluated separately for each TKI cohort

Study design

Phase IV observational trial
- Duration: 2 year per TKI
There will be different cohorts, every TKI will be assessed separately. (erlotinib, gefitinib, afatinib, osimertinib, crizotinib, ceritinib, alectinib, lorlatinib and brigatinib). For every TKI there is a WBRT (N=10) and a SRT (N=10) cohort. As osimertinib also became registered for the first line treatment of EGFR mutated NSCLC (previously only for EGFR T790M) and prognosis including brain progression rates, is different for these subgroups, two separate osimertinib groups will be made (osimertinib first line, WBRT [N=10] and SRT [N=10], and osimertinib beyond first line for T790M+ patients, WBRT [N=10] and SRT [N=10]. Patients are already treated with a TKI, the TKI is not part of the study. Patients are already scheduled for WBRT/SRT, this decision is not influenced by this trial. When a new TKI becomes available a new cohort will open and an amendment will be presented.
o Duration per patient will be approximately 6 months.
o Normally about 20 patients with a driver mutation are seen in 1 year at 1 centre. Of these patients about 5 will develop brain metastasis and are eligible for the study. There will be 6 centres that participate.
- Setting: the 6 centres (MUMC, VUmc, NKI/ AVL, UMCG, Erasmus MC, Radboud MC) that are NVALT acknowledged as specialised driver mutation centers.

Study burden and risks

The MRI and questionnaires that are used in this study are non-invasive except for a venapuncture to administer gadolinium-contrast for the MRI (and half of the MRIs are standard care for these patients). The risks of a MRI-scan are negligible because it is a magnetic field and does not involve ionizing. The

venapuncture can cause a hematoma. The MRI will be performed twice (once already as standard care), preferably the same day as regular visits. Time per MRI is approximately 30 minutes. The neurocognitive testing will take about 60 minutes. This will also be done at the same day as regular visits.
Obtaining CSF by lumbar puncture is optional and is an invasive investigation. It will take about 10 minutes and will be done by an experienced neurologist. As a possible complication of the puncture a temporary headache can occur.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

To be eligible to participate in this study, a patient must meet all of the following criteria:
- Stage IV NSCLC with driver mutation, treated with TKI, development of brain

metastases during TKI treatment
- Indication for cranial radiotherapy determined by treating physician and radiation oncologist
- Age >= 18 years
- Ability to understand neurocognitive testing
- Written informed consent

Exclusion criteria

A potential patient who meets any of the following criteria will be excluded from participation in this study:
- Prior radiotherapy to the brain when this precludes new radiotherapy.
- Neurologic/psychiatric illnesses (such as Alzheimer*s disease)
- Claustrophobia
- Metal implants or other contra-indication for MRI
- Inability to lie supine for 30 minutes time (MRI)

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-07-2018
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO

Date:	09-05-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-01-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-04-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-01-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-03-2025
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 28884
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL63377.068.17