PET imaging of [18F]dabrafenib distribution and kinetics in brain metastasis.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON44943

Source
ToetsingOnline

Brief title
[18F]dabrafenib molecular imaging

Condition

- Metastases

Synonym
advanced melanoma, Metastatic melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Novartis,Novartis (Nederland)

Intervention

Keyword: [18F]dabrafenib, brain metastases, molecular imaging

Outcome measures

Primary outcome

The main study parameters are standardized uptake value and distribution volume. The last derived from kinetic modeling using the arterial input of the tracer and plasma metabolites measurements.

Secondary outcome

Both inter- and intrapatient heterogeneity will be determined for the SUV's of the diffent lesions seen on PET. For response evaluation anatomical measurements of target lesions according to the RECIST 1.1 criteria will be used. The response will be correlated to drug accumulation (absolute uptake of tracer). In addition, immunohistochemical staining for B-raf and mutational load of BRAF measured by ddPCR will be correlated to absolute tracer uptake.

Study description

Background summary

Dabrafenib is an oral protein tyrosine kinase inhibitor which specifically targets mutated BRAF protein. It is used in the treatment of metastatic melanoma with evidence of a BRAF V600 mutation in genomic material. However, in this group of patients often a heterogenic response to treatment is seen. Heterogeneity in drug accumulation in the tumor could be responsible for the observed differences in treatment response between lesions and between patients. Besides poor tumor accumulation of the drug, heterogeneous expression of the drug target B-Raf protein between patients and between lesions within a single patient could account for heterogeneity in treatment response.
PET imaging with radioactively labeled carrier-added [18F]dabrafenib (low specific activity) as the tracer might be a useful tool to show the distribution pattern and kinetics of the native drug; in particular PET can be

used to determine if dabrafenib can cross the blood-brain barrier (BBB) and accumulate in brain metastases.
Since the behavior of [18F]dabrafenib in patients is hitherto unknown, first a feasibility study is needed. In this feasibility study, we will use low specific activity [18F]dabrafenib, for which a labeling procedure has already been developed, to determine the whole body distribution and kinetics in brain metastases in metastatic BRAF V600 mutation positive melanoma patients.

Study objective

Primary objective is to determine the absolute uptake (Standardized uptake value (SUV)) and kinetics (time-activity curves) of [18F]dabrafenib in normal brain and brain metastasis.
Secondary objectives are to analyze heterogeneity in [18F]dabrafenib accumulation and kinetics between different lesions within the brain, between lesions in different organs and between lesions in different patients. Other secondary objectives are to correlate drug accumulation to response to treatment (based on follow up scans after 4 weeks) and to correlate tracer uptake to immunohistochemical staining of biopsy samples with monoclonal antibodies against mutated B-Raf protein. In addition, the correlation between mutational load of BRAF as measured with Droplet Digital PCR and tracer uptake is a secondary objective.

Study design

This study is a feasibility study for the use of [18F]dabrafenib as a PET tracer, in 10 patients. Patients will receive a dynamic PET scan of the brain with bloodsampling and a static total body PET scan before start with dabrafenib. The PET-scan will be accompanied by a CT scan of chest and abdomen and a MRI scan of the brain. For study purposes one venous blood sample of 10ml will be obtained. If feasible a biopsy will be taken from an easy accesible lesion.

Intervention

A [18F]dabrafenib PET/CT scan and an MRI scan of the brain will be performed at baseline, which is 7 days or less before the start of treatment with oral dabrafenib. The PET procedure commence with the injection of approximately 200 MBq [18F]dabrafenib, which is followed by a 60 minutes dynamic PET scan of the brain and thereafter a total-body PET scan. During the dynamic PET scan of the brain, arterial blood sampling and analysis of plasma metabolites will be performed. Treatment response will be monitored as part of the regular treatment (CT for thorax/abdomen and MRI for brain) after 4 weeks.

Study burden and risks

Patients who will participate in this study will receive a dynamic PET/CT scan of the brain, a static total-body PET/CT scan and an MRI scan of the brain at baseline. After 4 weeks they receive a CT scan of chest and abdomen and a MRI scan of the brain as part of regular treatment. The PET scan, which is a study procedure, carries a radiation burden of 4.1 mSv. This constitutes an intermediate risk, based on criteria of the International Commission on Radiological Protection. For the purpose of pharmacokinetic modeling, an arterial catheter will be placed which is an invasive procedure. Expected adverse events will be identical to that of unlabeled dabrafenib. Besides PET imaging, a single venous blood sample will be taken which will give minor discomfort. In addition, patients will be asked to give consent for a biopsy. This is an invasive procedure. The presence of easily accessible lesions is precondition. Although biopsies are generally considered to be safe, it could be a painful intervention and carries the risk of bleeding at the puncture site. Patients do not directly benefit from the study, but their participation helps to get more insights in the pharmacokinetics of dabrafenib and its role in the treatment of brain metastases.

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

1. Has signed informed consent.
2. Older than 18 years of age.
3. Histologically confirmed cutaneous metastatic melanoma (Stage IV), including confirmed brain metastases.
4. BRAF mutation-positive (V600 E/K) melanoma as determined by standardized genetic testing.
5. Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1).
6. Eligible for standard treatment with dabrafenib.
7. No contraindication for performing a CT scan.
8. No contraindication for performing a MRI scan of the brain.
9. Women with child-bearing potential and men with reproductive potential must be willing to practice acceptable methods of birth control from 14 days prior to randomization, throughout the treatment period and for 4 weeks after the last dose of study treatment.
10. Women of child-bearing potential must have a negative serum pregnancy test (*-HCG) within 14 days of first dose of study treatment.

Exclusion criteria

1. Treatment with a BRAF or MEK inhibitor.
2. Known immediate or delayed hypersensitivity reaction to dabrafenib or excipients.
3. Use of other investigational drugs within 28 days (or five half-lives, whichever is shorter; with a minimum of 14 days from the last dose) preceding the first dose of study treatment and during the study.
4. Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Grade 2 or higher from previous anti-cancer therapy, except alopecia.
5. Any serious or unstable pre-existing medical conditions (i.e, diabetes mellitus, hypertension, etc), psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol; or unwillingness or inability to follow the procedures required in the protocol.
6. Altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent, unless a legally acceptable representative could provide informed consent.
7.Pregnant or nursing females.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-12-2016
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	18-04-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-05-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-11-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-12-2017
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
EudraCT	EUCTR2014-004667-21-NL
ClinicalTrials.gov	NCT02700763
CCMO	NL50793.042.16