The TRAIN study: Trametinib in neurofibromatosis type 1 related symptomatic plexiform neurofibromas

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Primary objective: Response to trametinib treatment defined as a tumor volume decreases from baseline of >=20%, monitored by using volumetric MRI analysis. Secondary objectives are: patient reported outcomes of pain and disability and quality of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON49019

Source
ToetsingOnline

Brief title
TRAIN study: Trametinib in plexiform neurofibroma

Condition

- Neurological disorders congenital
- Nervous system neoplasms benign
- Nervous system neoplasms benign

Synonym
benign tumors, Neurofibroma

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Novartis,Stichting NF

Intervention

Keyword: Neurofibromatosis type 1, Plexiform neurofibroma, Trametinib

Outcome measures

Primary outcome

To determine whether trametinib can induce shrinkage in plexiform neurofibromas lesions. Response to treatment is defined as a tumor volume decreases from baseline of >=20%, monitored by using volumetric MRI analysis

Secondary outcome

Neurofibromatosis type 1 patients with plexiform neurofibromas derive clinical benefit from trametinib treatment:

• Patient reported outcomes of pain and disability and quality of life

• The effect of trametinib on disfigurement

• Safety and tolerability of trametinib

• The duration of response

• Incidence of surgical interventions

Study description

Background summary

Neurofibromatosis type 1 is one of the most common neuro-genetic diseases. Approximately half of the patients with neurofibromatosis type 1 have plexiform neurofibromas. Besides severe cosmetic problems, the plexiform neurofibromas cause neurological deficit, severe pain and a 8-12% lifetime risk of developing a Malignant Peripheral Nerve Sheath Tumor.
Up till now surgery is the only standard treatment option for plexiform neurofibromas. Complete resection is often impossible due to extensive and invasive growth of the plexiform neurofibromas. Therefore, systemic treatment

options for plexiform neurofibromas in neurofibromatosis type 1 are a highly unmet medical need.
Recent data suggests that children with inoperable neurofibromatosis type 1 related plexiform neurofibromas benefited from long-term treatment with an oral selective inhibitor of MAPK kinase (MEK) 1 (selumetinib) without having excess toxic effects. Treatment with selumetinib resulted in a response rate of 71% in 24 children. Following this observation we now propose to perform a study with trametinib, a MEK1/2 inhibitor, in adult neurofibromatosis type 1 patients with symptomatic plexiform neurofibromas.

Study objective

Primary objective: Response to trametinib treatment defined as a tumor volume decreases from baseline of >=20%, monitored by using volumetric MRI analysis. Secondary objectives are: patient reported outcomes of pain and disability and quality of life, the effect of trametinib on disfigurement, safety and tolerability of trametinib, the duration of response and the incidence of surgical interventions

Study design

This is a non-randomized, open-label, single arm phase 2 study to determine whether we can achieve a response for neurofibromatosis type 1 patients with symptomatic plexiform neurofibromas using trametinib.

Intervention

Trametinib 2mg daily, orally, continuous until progression

Study burden and risks

Generally, the side-effects of trametinib are mild and manageable. The main burden for the patients are 4 weekly visits during therapy and every 3 months thereafter until progression. Blood samples will be taken every 4 weeks during therapy. 6 monthly a MRI, quality of life forms and physical examination will be done until progression. Needle biopsies from the (largest) index plexiform neurofibromas will be performed pre-treatment and at 12 weeks. A needle biopsy is minimally invasive and is typically a safe procedure.
Before the start of therapy, after 4 weeks and every 12 weeks, an echocardiography will be done to measure the ejection fraction. Sometimes a MUGA scan will be made for logistical reasons. The amount of radioactivity used in the MUGA scan is very low and has no harmful consequences.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Patient with (mosaic) NF1
2. Patients with a clinically significant symptomatic plexiform neurofibroma, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. This will be determined by the treating physician.
3. Signed, written informed consent
4. Age: 18 or higher
5. Karnofsky performance level of >=70%
6. No standard treatment options = inoperable plexiform neurofibroma. Plexiform neurofibroma that cannot be surgically completely removed without risk for

substantial morbidity due to invasiveness, high vascularity or encasement of, or close proximity to, vital structures of the plexiform neurofibroma.
7. At least one measurable plexiform neurofibroma, defined as a well-demarcated lesion of at least 3 cm measured in one dimension.
8. Able to swallow and retain orally administered medication.
9. Female Subjects of Childbearing Potential must have negative pregnancy test within 7 days prior study treatment and agrees to use highly effective contraception
10. Normal hematological function: Hemoglobin (Hb)>=6 mmol/l, absolute neutrophil count (ANC)>=1.5x109/l, and platelets>=100x109/l
11. Normal hepatic function: bilirubin <1.5x the upper limit of normal (UNL), unless gilbert then: bilirubin <3xUNL and AST/ALT <5xUNL
12. Normal renal function: creatinine <1.5xUNL

Exclusion criteria

1. Prior treatment with MEK inhibitor(s)
2. Inability to undergo MRI and/or contraindication for MRI examinations
3. History of a malignancy within 5 years of inclusion, except squamous cell carcinoma of the skin, cervical premalignant lesions and other curatively treated malignancy
4. Prior radiotherapy less than 6 weeks prior to enrollment
5. Prior major surgery less than 4 weeks prior to enrollment
6. An investigational agent within the past 30 days.
7. Enzyme-inducing anticonvulsants, anti-coagulants (including platelet aggregation inhibitors) or other prohibited medication(s) or requirement for prohibited medications
8. Left ventricular dysfunction, New York Heart Association Class II, III, or IV heart failure, acute coronary syndrome within the past 6 months, clinically significant uncontrolled arrhythmias, and uncontrolled hypertension.
9. A history of retinal vein occlusion (RVO) or predisposing factors for RVO, including uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes
10. Risk factors for gastrointestinal perforation, including history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medications with a recognized risk of gastrointestinal perforation
11. Any evidence of severe or uncontrolled systemic disease, active infection, active bleeding diatheses, or renal transplant, including any patient known to have hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) will be excluded.
12. Refractory nausea and vomiting, chronic gastrointestinal diseases (e.g., inflammatory bowel disease), or significant bowel resection that would preclude adequate absorption.
13. Any serious and/or unstable pre-existing medical disorder, psychiatric

disorder, or other conditions that could interfere with subject*s safety
14. Known severe hypersensitivity to trametinib or any excipient of trametinib or history of allergic reactions attributed to compounds of similar chemical or biologic composition to trametinib
15. Pregnant, lactating or actively breastfeeding female subjects

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-07-2020
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mekinist
Generic name:	trametinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	17-10-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	30-10-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-06-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2019-001317-16-NL
CCMO	NL69517.078.19