TRAmetinib In Neurofibromatose type 1 related symptomatic plexiform neurofibroma

No registrations found.

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

Summary

ID

NL-OMON28237

Source
Nationaal Trial Register

Brief title
TRAIN

Health condition

Neurofibromatosis type 1, NF1, plexiform neurofibroma

Sponsors and support

Primary sponsor: Erasmus MC
Source(s) of monetary or material Support: Stichting NF and Novartis

Intervention

Outcome measures

Primary outcome

Objective Response Rate

Secondary outcome

Patient reported outcomes of pain and disability and quality of life
The effect of trametinib on disfigurement.
Adverse events reporting according to CTCAEv5.0
Time to first significant progression defined as >20% volumetric growth of the index lesion(s)
Incidence of surgical interventions

Study description

Background summary

Rationale: Neurofibromatosis type 1 (NF1) is one of the most common neuro-genetic diseases. Approximately half of the patients with NF1 have plexiform neurofibromas (PNF).1 Besides severe cosmetic problems, the PNF cause neurological deficit, severe pain and a 8-12% lifetime risk of developing a Malignant Peripheral Nerve Sheath Tumor (MPNST).2, 3 Up till now surgery is the only standard treatment option for PNF. Complete resection is often impossible due to extensive and invasive growth of the PNF. Therefore, systemic treatment options for PNF in NF1 are a highly unmet medical need.
Recent data suggests that children with inoperable neurofibromatosis type 1 related PNF benefited from long-term treatment with an oral selective inhibitor of MAPK kinase (MEK) 1 (selumetinib) without having excess toxic effects.4 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 NF1 patients with symptomatic PNF.
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 NF1 patients with symptomatic PNF using trametinib.
Study population: 30 adult patients (age >17 years) with (mosaic) NF1 with inoperable symptomatic plexiform neurofibromas
Intervention: Trametinib 2mg daily, orally, continuous until progression
Main study parameters/endpoints: The primary endpoint is response to treatment defined as a tumor volume decreases from baseline of ≥ 20%
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: 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 PNF will be performed pre-treatment and at 12 weeks. A needle biopsy is minimally invasive and is typically a safe procedure.

Study objective

Trametinib can induce shrinkage in neurofibromatosis type 1 related plexiform neurofibromas. Response to treatment is defined as a tumor volume decreases from baseline of ≥20%, monitored by using volumetric MRI analysis.

Study design

Disease will be assessed by volumetric MRI every 24 weeks until documented progression. Safety profile of the treatment will be assessed every 4 weeks during therapy and every 3 months after the end of treatment. Furthermore, quality of life assessments takes place every 24 weeks using questionnaires.

Intervention

Trametinib 2mg daily, orally, continuous until progression, patients refusal to continue the medication with trametinib or unacceptable side effects of trametinib.

Contacts

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Eligibility criteria

Inclusion criteria

1. Patient with (mosaic) NF1
2. Patients with a clinically significant symptomatic plexiform neurofibroma (PNF), 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 PNF
PNF 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 PNF.
7. At least one measurable PNF, 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 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):	07-07-2020
Enrollment:	30
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Plan description
N/A

Ethics review

Positive opinion

Date:	27-09-2019
Application type:	First submission

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
NTR-new	NL8050
Other	METC Erasmus MC : MEC-2019-0463

Study results

Summary results
N/A