Trial with melanoma patients who are treated with dabrafenib and trametinib to make the tumor smaller, so it can be surgically removed.

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For patients with stage III-IV irresectable melanoma who have at most 3 metastases, the tumor can be reduced in size by treating with dabrafenib and trametinib for 8 weeks. After this reduction, complete surgery of the tumor could be made possible.

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON25911

Bron
NTR

Verkorte titel
REDUCTOR

Aandoening

Stage III-IV Melanoma

Ondersteuning

Primaire sponsor: Antoni van Leeuwenhoek ziekenhuis
Overige ondersteuning: GSK

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Ability of dabrafenib + trametinib treatment to downsize melanoma tumor masses to enable R0 resection.

Toelichting onderzoek

Achtergrond van het onderzoek

In this phase II study patients with BRAF mutated, prior unresectable stage III or oligometastatic stage IV melanoma will receive the combination dabrafenib with trametinib neoadjuvant for 8 weeks. The purpose is to reduce the tumor in size, so to make complete surgical resection possible. In this monocenter study 25 patients will be treated in The Netherlands Cancer Institute (Antoni van Leeuwenhoek). Besides determining the response of these patients also extensive translational research will be performed on the obtained tissue.

Doel van het onderzoek

For patients with stage III-IV irresectable melanoma who have at most 3 metastases, the tumor can be reduced in size by treating with dabrafenib and trametinib for 8 weeks. After this reduction, complete surgery of the tumor could be made possible.

Onderzoeksopzet

The trial exists of 2 phases. First 14 patients will be treated (after about 1 year), response in those patients will be measured. If for more than 4 patients complete resection has been accomplished, another 9 patients will be treated. If not, the study will stop.

Onderzoeksproduct en/of interventie

Patients will be treated with dabrafenib and trametinib for 8 weeks. Biopsies will be taken at screening, after 2 weeks and after 8 weeks.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1.Has provided signed informed consent.

2.Unresectable stage III melanoma (documented and based on MSD) or stage IV melanoma with ≤ 3 resectable metastases/organ site.

3.Pathologically confirmed BRAF mutation-positive (V600E/K) melanoma as determined via in-house testing with a BRAF mutation assay.

4.Are treatment naïve for unresectable melanoma.

5.For whom the intended operation is considered to offer a chance of cure or substantial palliation.

6.Evaluable disease by CT/MRI or PET with ≤ 3 metastases/organ sites.

7.Age ≥18 years of age.

8.Able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

9.Women with child-bearing potential and men with reproductive potential must be willing to practice acceptable methods of birth control during the study.

10.Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to the first dose of study treatment.

11.Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1.

12.Must have adequate organ function as defined by the following screening values (Retesting of borderline screening organ function. will be allowed. Treatment with transfusion, growth factors to meet eligibility criteria will not be allowed):

• Absolute neutrophil count (ANC) ≥1.2x109/L

• Hemoglobin ≥5.6 mmol/L

• Platelets ≥75x109/L

• Serum bilirubin ≤1.5 x upper limit of normal (ULN)

• Albumin ≥2.5 g/dL

• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5xULN

• Serum creatinine ≤1.5 mg/dL (If serum creatinine is >1.5 mg/dL, calculate creatinine clearance using standard Cockcroft and Gault method. Creatinine clearance must be > 50 mL/min.

• Prothrombin time (PT)/International normalized ratio (INR) and partial thromboplastin time (PTT) ≤1.5xULN

• Left ventricular ejection fraction ≥ institutional lower limit of normal.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Known ocular or primary mucosal melanoma.

2. Use of any investigational anti-cancer or other drug within 28 days or 5 half-lives, whichever is longer, preceding the first dose of dabrafenib + trametinib.

3. Current use of a prohibited medication or is expected to require any of these medications during treatment with dabrafenib and trametinib.

4. Any major surgery, radiotherapy, or immunotherapy within the last 4 weeks.

5. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption of drugs.

6. A history of glucose-6-phosphate dehydrogenase (G6PD) deficiency.

7. A history of other malignancy. Subjects who have been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible

8. History of alcohol or drug abuse within 6 months prior to screening.

9. 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.

10.Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (with the exception of chronic or cleared HBV and HCV infection which will be allowed).

11.The following cardiac abnormalities:

•A QT interval corrected for heart rate using Bazett's formula ≥ 480 msec;

•A history or evidence of current clinically significant uncontrolled arrhythmias; subjects with atrial fibrillation controlled for > 30 days prior to randomization are eligible.

•A history (within 6 months prior to randomization) of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty;

•A history or evidence of current ≥ Class II congestive heart failure as defined by the New York Heart Association (NYHA) guidelines;

•Treatment refractory hypertension defined as a blood pressure of systolic > 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy;

•Patients with intra-cardiac defibrillators or permanent pacemakers;

•Known cardiac metastases;

•Abnormal cardiac valve morphology (≥grade 2) documented by echocardiogram (subjects with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.

12.A history or current evidence/risk of retinal vein occlusion (RVO) or CSR including:

•Presence of predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of

hyperviscosity or hypercoagulability syndromes); or

•Visible retinal pathology as assessed by ophthalmic examination that is considered a risk factor for RVO or CSR such as:

13.Evidence of new optic disc cupping;

•Evidence of new visual field defects on automated perimetry;

• Intraocular pressure >21 mmHg as measured by tonography.

14.Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO).

15.Pregnant or lactating female.

16.Patients with CNS metastases.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Factorieel
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-03-2014
Aantal proefpersonen:	25
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	20-06-2014
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL4519
NTR-old	NTR4654
Ander register	Netherlands Cancer Institute (NKI) : N13NDT

Resultaten