Cytoreductive treatment of dabrafenib combined with trametinib to allow complete surgical resection in patients with BRAF mutated, prior unresectable stage III or IV melanoma

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Primary objectives: To assess the ability of dabrafenib + trametinib treatment to downsize melanoma tumor masses to enable R0-resection. Secondary objectives: Recurrence free survival; time-to-next treatment, overall survival.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON38944

Source
ToetsingOnline

Brief title
Presurgical MAPK inhibition in stage III-IV melanoma, REDUCTOR

Condition

- Skin neoplasms malignant and unspecified

Synonym
maligne melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: GlaxoSmithKline

Intervention

Keyword: cytoreduction, Dabrafenib, Melanoma, Trametinib

Outcome measures

Primary outcome

The primary endpoint of this study is the % of patients in whom an R0-resection could be performed. This is measured by the pathologist, who handles the resection material (no positive margins) and negative CT-scans. Patients that develop a CR on systemic treatment will of course be included in the analysis. The aim of the study is to enable R0 resection.

Secondary outcome

As the secondary endpoint recurrence-free survival will be assessed every 3 months by physical exam and CT-scan for 2 years, thereafter every 6 months for 2 year, and once in year 5. Thereafter by physical exam only. This will be assessed only in patients that undergo radical surgery. For patients not undergoing surgery, PFS will be assessed.
Time to next treatment is defined as the moment the study treatment starts until start of any following treatment (surgery, RT or systemic treatment) for new lesions. This will be measured in all patients, but patients will be stratified for undergoing surgery or not undergoing surgery. Overall survival will be measured using Kaplan-Meier estimation for the total group of patients as well, again stratified for patients undergoing surgery or no surgery.

Study description

Background summary

For patients with macroscopic regional metastatic melanoma complete surgical resection is considered the standard-of-care, in some cases followed by locoregional radiotherapy in order to maintain local control. However, about 5% of these patients present with one or a few locoregional tumor sites that are so extensive that the tumor is deemed unresectabel, despite the fact that the disease is still regional. If surgical therapy could be made possible through a reduction of the size of such lesions and would imply that a cure (or substantial palliation) could be pursued, such patients may benefit from cytoreductive systemic treatment with a potent anticancer drug.
Clinical trials with patients with BRAF V600 mutated stage IV disease have shown impressive objective response rates of around 50% with selective inhibitors of mutated BRAF, and another 30% of patients may benefit with less than 30% shrinkage of total tumor burden. Importantly, BRAF inhibitors act very fast after initiation of treatment and important metabolic responses have been demonstrated as early as 2 weeks after initiation of treatment using PET-imaging. At 6 weeks after initiation of treatment in the vast majority of patients, regression of tumors are recorded by CT-scan. The combination of both BRAF inhibition and MEK inhibition may improve the efficacy of BRAF inhibition only. Preliminary results of a phase II study combining dabrafenib and MEK inhibitor trametinib point in the direction of improved efficacy (higher response rate, including more patients developing complete remissions), and less toxicity compared to either drug alone. Therefore, the combined use of dabrafenib (GSK2118436) and trametinib (GSK1120212) poses an excellent opportunity to be used as a pre-surgical modality in primary unresectable stage III/IV disease. Because of the early response induction, we expect that in a period of 8 weeks, it should become clear whether the tumor has shrunk enough to enable surgery with curative intent. Therefore, the primary objective of this study is to enable R0 resection.
We hypothesize that the feasibility of this approach can be tested in a small two stage designed phase II trial (n=25 pts).

Study objective

Primary objectives: To assess the ability of dabrafenib + trametinib treatment to downsize melanoma tumor masses to enable R0-resection.

Secondary objectives: Recurrence free survival; time-to-next treatment, overall survival.

Study design

The study is designed as a two-stage phase II trial in which a total of 25 patients will be treated if the response in the first 14 patients is sufficient.
Patients with primary unresectable stage III or IV disease are eligible for this trial. Criteria to define these patients have not been standardized and therefore are considered the outcome of a documented multi-surgeon decision (MSD).
Once eligible according the MSD, after having signed the ICF, patients that fulfill the eligibility criteria will undergo a tumor biopsy and blood sampling for further translational research. A PET-CT-scan will be performed and the patient will start with dabrafenib (dose 150mg twice daily) + trametinib (dose 2 mg once daily). At t=2wks and t=8 wks another biopsy and a PET-CT scan will be performed. At t=8 weeks, patients will be discussed in a multidisciplinary meeting and resection with curative intend will follow if the tumor has been downsized sufficiently, if not dabrafenib + trametinib will be continued until disease progression.

Intervention

Prior to inclusion patients will undergo PET-CT-scan and MRI-scan as baseline measurement. A biopsy will be taken before start of treatment. Patients will be treated with dabrafenib (GSK2118436), 150 mg BID and trametinib (GSK1120212), 2 mg QD for a period of 8 weeks. At time point 2 weeks a PET/CT scan will be made and a 2nd biopsy will be taken and stored. After 4 weeks the patients will be examined by their melanoma surgeon.
At time point 8 weeks patients will undergo another PET-CT, and if required an MRI scan, to measure response. If the tumor has been downsized sufficiently and no new lesion has occurred, the operation will be planned within the next 2-3 weeks. If the tumor is still unresectable, the patient will continue treatment with dabrafenib + trametinib until disease progression. At time point 8 weeks a 3rd biopsy will be taken if no resection can take place.

Study burden and risks

The prognosis of patients with unresectable stage III disease is comparable to that of patients with stage IV disease. The median overall survival (OS) for the total group is most likely still less than one year. Only recently, for patients with a BRAF V600 mutated melanoma, which is present in about 50% of patients, the median OS has surpassed the one year (13,4 months for vemurafenib treated patients in the BRIM3 trial). Based on a small phase I/II study in BRAF mutated melanoma patients that were treated with the combination of dabrafenib and trametinib, with a PFS of 9,4 months, it may be expected that the median OS can be improved further. For patients with unresectable stage III disease or limited stage IV disease, the option to be treated with a highly active drug combination, which may lead to change of the disease from unresectable to operable, could lead to even further improvement of the overall survival. This

patient group however is small, probably not exceeding 5% of the total patient population with stage III or limited stage IV disease.
Compared to single drug treatments, the toxicity of this drug combination is rather mild, with pyrexia being one of the most frequently reported toxicities. Pyrexia is however, well manageable (based on previous studies). In addition, outside of this trial, these patients would be eligible for a trial with BRAF inhibitor plus or minus MEK inhibitor, and therefore would be exposed to one or two drugs anyway. The extra burden for the patients in this trial are the biopsies and extra blood samples that are taken prior to and at 2 and for some patients 8 weeks after initiation of treatment, and PET-scans that are made during this trial. We consider these interventions acceptable, especially in relation to the severity of this disease.

Contacts

Public
Nederlands Kanker Instituut

Plesmanlaan 121
Amsterdam 1066CX
NL
Scientific
Nederlands Kanker Instituut

Plesmanlaan 121
Amsterdam 1066CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients have provided signed informed consent.
2. Patients have unresectable stage III melanoma (documented and based on MSD) or stage IV melanoma with <= 3 resectable metastases/organ site.
3. Patients have pathologically confirmed BRAF mutation-positive (V600E/K) melanoma as determined via in-house testing with a BRAF mutation assay.
4. Patients are treatment naïve for unresectable melanoma.
5. Patients for whom the intended operation is considered to offer a chance of cure or substantial palliation.
6. Patients have evaluable disease by CT/MRI or PET with <= 3 metastases/organ sites.
7. Patients are >=18 years of age.
8. Patients are able to swallow and retain oral medication.
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. Patients have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1.
12. Patients must have adequate organ function as defined in the protocol. Treatment with transfusion, growth factors to meet eligibility criteria will not be allowed.

Exclusion criteria

1. Patients with known ocular or primary mucosal melanoma.
2. Patients who used 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. Patients who currently use a prohibited medication or are expected to require any of these medications during treatment with dabrafenib and trametinib.
4. Patients who had any major surgery, radiotherapy, or immunotherapy within the last 4 weeks.
5. Patients with active gastrointestinal disease or other condition that will interfere significantly with the absorption of drugs.
6. Patients with a history of glucose-6-phosphate dehydrogenase (G6PD) deficiency.
7. Patients with 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. Patients with a history of alcohol or drug abuse within 6 months prior to screening.
9. Patients with 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. Patients with the cardiac abnormalities as defined in the protocol.
11. Pregnant or lactating female.
12. Patients with CNS metastases.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-08-2014
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mekinist
Generic name:	trametinib
Product type:	Medicine
Brand name:	Tafinlar
Generic name:	dabrafenib

Ethics review

Approved WMO Date:	24-09-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	04-12-2013
Application type:	First submission

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2013-002616-28-NL
CCMO	NL45261.031.13