A Phase II, Open-Label, Multicenter Study of Vemurafenib plus Cobimetinib (GDC-0973) in Unresectable Stage IIIc or Stage IV Melanoma; Response Monitoring and Resistance Prediction with Positron Emission Tomography and Tumor Characteristics.

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To study whether either early 18F-FDG or 18F-FLT PET is superior in detecting response to treatment with the combination of vemurafenib plus cobimetinib (GDC-0973) compared to standard response assessment with CT and to evaluate whether, and which,...

Ethical review	Approved WMO
Status	Pending
Health condition type	Skin neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON44689

Source
ToetsingOnline

Brief title
Vemurafenib plus Cobimetinib in Metastatic Melanoma; REPOSIT.

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Werkgroep Immunotherapie Nederland voor Oncologie (WIN-O)
Source(s) of monetary or material Support: Roche Medical BV

Intervention

Keyword: Melanoma, Positron Emission Tomography, Tumor characteristics, Vemurafenib/cobimetinib (GDC-0973)

Outcome measures

Primary outcome

• Progression Free survival (PFS)

• Correlation between changes of metabolic tracer uptake on PET and of size on diagnostic CT according to RECIST 1.1 from baseline, Day 14/15 Cycle 1, Day 21 Cycle 2 and at the time of progression.

• Diagnostic accuracy and best cut-off values of PET at Day 14/15 Cycle 1 and Day 21 Cycle 2 for distinguishing responders from non-responders.

• Investigation of the continuous parameters of PET in association with Progression Free Survival.

Secondary outcome

• Correlation of PET-imaging with 18F-FDG PET and 18F-FLT PET between baseline and Day 14/15 Cycle 1 by means of Standardized Uptake Value.

• Correlation of PET-imaging with 18F-FDG PET and 18F-FLT PET at the time of progression by means of Standard Uptake Value.

• Correlation between 18F-FDG/FLT uptake and immunohistochemical analysis in responders and non responders early after the initiation of therapy.

• Correlation between 18F-FDG/FLT uptake and resistance by means of diagnostic CT and PFS.

• Best quantification of metabolic imaging. Various quantitative measures of radiotracer uptake determined in RECIST 1.1 target lesions, correlated to PFS and OS.

• Correlation between genetic analysis and resistance in terms of RECIST1.1 criteria on diagnostic CT and PFS.

• Correlation between phosphoprotein profiles and resistance in terms of RECIST1.1 criteria on diagnostic CT and PFS.

• Overall Survival (OS)

• Drug level monitoring of vemurafenib and cobimetinib (GDC-0973) at Day 15 Cycle 1 compared to tumor response (RECIST1.1 criteria) and PFS.

• Drug level monitoring of vemurafenib and cobimetinib (GDC-0973) at Day 15 Cycle 1 compared to 18F-FDG/FLT uptake.

• ECOG Performance status

Study description

Background summary

Molecular targeted therapy with BRAF inhibitor vemurafenib is currently used as first line treatment for patients with unresectable stage IIIc or metastatic melanoma harboring the BRAFV600 mutation, which is present in about 50% of melanoma patients. Despite the improvement in Progression Free Survival (PFS) en Overall Survival (OS) compared to dacarbarzine, acquired resistance that develops in virtually all patients treated with vemurafenib is a great concern. Combining a BRAF inhibitor with a MEK inhibitor that targets the MAPK pathway further downstream, however, may postpone acquired resistance to BRAF inhibition and recent studies in which both MEK inhibitors and BRAF inhibitors are combined are very promising.

In a phase IB trial preliminary efficacy of vemurafenib with cobimetinib (GDC-0973), a highly selective inhibitor of MEK1 seems encouraging with an initial response rate of 85% and currently a phase III study of vemurafenib versus vemurafenib plus cobimetinib (GDC-0973) in BRAFV600 mutation positive patients with advanced stage melanoma is underway. Currently, 3 different BRAF- and MEK-inhibitors are under investigation in phase 3 trials. It is expected that in the near future combined BRAF and MEK inhibition will be standard of care for patients with BRAFV600 mutated metastatic melanoma.
Diagnostic CT cannot assess reduction in tumor size within days after the initiation of therapy and anatomic size does not provide information about the development of therapy response or resistance at a molecular level. It has been clearly demonstrated that alterations in metabolism occur earlier than anatomical size reduction after the initiation of therapy. Molecular imaging with PET visualizes metabolic activity in tumors and is a sensitive method to detect alterations in cell metabolism, even shortly after the start of therapy. 18F-Fluorodeoxyglucose (18F-FDG) is used to visualize glucose metabolism, whereas 18F-Fluoro-3*-deoxy-3*L-fluorothymidine (18F-FLT) is used to visualize proliferation. In preclinical mouse models 18F-FLT appears to predict response or resistance to therapy better than 18F-FDG. However, so far only 18F-FDG PET has been used to monitor response to vemurafenib in some BRAFV600 mutated metastatic melanoma patients, showing a rapid decline of 18F-FDG within 2 weeks following treatment. Preclinical studies and the observation that melanoma is a highly proliferative malignancy in most patients suggest that 18F-FLT might be the radiopharmaceutical of first choice in this setting.
By detecting these metabolic alterations, responders might be distinguished from non-responders at an earlier phase compared with anatomical imaging with CT. This way, unnecessary expensive treatment of combined BRAF/MEK-inhibitor therapy and its side effects can be prevented in patients who will not benefit from this therapy. In addition, therapy could be adapted to new targeted-therapies (e.g. Erk-inhibitors or PI3-kinase inhibitors) or immunotherapies at an earlier stage.
We propose a single arm explorative phase II clinical trial in 90 subjects with advanced stage melanoma harbouring a BRAFV600E of BRAFV600K mutation. We will combine PET imaging and molecular diagnostics in order to monitor response to treatment with vemurafenib plus cobimetinib (GDC-0973), examine development of resistance and correlate changes in metabolic/proliferative activity with extend of target inhibition in tumor tissue.

Study objective

To study whether either early 18F-FDG or 18F-FLT PET is superior in detecting response to treatment with the combination of vemurafenib plus cobimetinib (GDC-0973) compared to standard response assessment with CT and to evaluate whether, and which, PET-imaging is superior in predicting resistance to vemurafenib/ cobimetinib (GDC-0973) treatment. These observations will be correlated to several key tumor characteristics.

Study design

This study is a multi-center open-label single arm explorative phase II clinical study.
Laboratory assessments, physical examination, dermatologic examination and cardiac evaluation will take place to monitor safety and side effects of vemurafenib/ cobimetinib (GDC-0973).
Patients included in this study will undergo additional imaging using 18F-FDG PET prior to treatment, two weeks after the initiation of therapy, after seven weeks and at progression to compare to regular CT-imaging to study whether PET-imaging is superior in predicting early response and in predicting resistance to vemurafenib/ cobimetinib (GDC-0973) treatment.
Blood samples will be collected for drug level monitoring of vemurafenib and cobimetinib (GDC-0973) and to correlate its pharmacokinetics with PET imaging and therapy response.
In twenty-five patients additional PET with 18F-FLT will be performed at baseline, 2 weeks and at progression to investigate which radiopharmaceutical (18F-FDG or18F-FLT) is superior in detecting early response and in predicting resistance.
Furthermore, in biopsies taken from forty patients prior to, and during treatment, histopathological tumor characteristics will be correlated with functional imaging. Next-generation sequencing, IHC analysis, gene expression analysis and phosphoproteomics will be performed in parallel to unravel new mechanisms of resistance to this drug.

Study burden and risks

The extra PET scans, biopsies and blood samples that are made or taken in this study will not interfere with the vemurafenib/ cobimetinib (GDC-0973) treatment protocol. The total number of performed procedures per patient can be fairly high, but this approach is needed to answer the clinically relevant questions at hand. Furthermore, the extra diagnostic procedures blend with the extensive monitoring protocol these patients already have when treated with vemurafenib, causing the extra time-effort as minimal as possible.
Considering the severity of the disease at the time of inclusion and the short life expectancy without the chance of cure, the radiation burden and side effects of these diagnostic procedures are negligible.
With the results of this study we will better understand the molecular behavior of stage IIIc and IV melanoma. We hope to identify responders from non-responders early after the initiation of therapy and reveal resistance to vemurafenib/ cobimetinib (GDC-0973). This way we can reduce the costs of unnecessary expensive treatment and prevent the risk of (severe) side effects of vemurafenib/ cobimetinib (GDC-0973). Furthermore, we believe that the results of this study will be fundamental for further optimizing treatment on an individual base.

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

• Patients with histologically confirmed melanoma, either unresectable stage IIIc or stage IV metastatic melanoma, as defined by AJCC 7th edition.
• Prior BRAF/MEK inhibition is allowed only when given for a period of at most 12 weeks prior to immunotherapy AND no progression is seen on ceCT at the time of discontinuation of BRAF/MEK inhibitor. Prior immunotherapy (including ipilimumab) is allowed.
• Documentation of BRAFV600E or BRAFV600K mutation-positive status in melanoma tumor tissue (archival or newly obtained tumor samples).
• Measurable disease per RECIST v1.1, which are accessible to biopsies.
• Biopsy lesion is within scan reach of diagnostic CT and PET-CT (thorax- abdomen-pelvis)
• ECOG performance status of 0 or 1.
• Male or female patient aged >= 18 years.
• Life expectancy >= 12 weeks.

• Adequate hematologic and end organ function within 14 days prior to first dose of study drug treatment.

Exclusion criteria

• History of prior RAF or MEK pathway inhibitor treatment longer than 21 weeks or shorter than 12 weeks but with clinical or radiological signs of progression.
• Palliative radiotherapy, major surgery or traumatic injury within 14 days prior to the first dose of study treatment.
• Active malignancy within the past 3 years other than melanoma that could potentially interfere with the interpretation of efficacy measures, except for patients with resected BCC or SCC of the skin, melanoma in-situ, carcinoma in-situ of the cervix, and carcinoma in-situ of the breast.
• History of or evidence of retinal pathology, clinically significant cardiac dysfunction, patients with symptomatic CNS lesions, renal or liver dysfunction as described in main protocol (REPOSIT NL48639.031.14).
• Pregnant, lactating, or breast-feeding.
• Unwillingness or inability to comply with study and follow-up procedures (i.e. severe anxiety disorder preventing PET/CT imaging.

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2014
Enrollment:	90
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cotellic
Generic name:	cobimetinib
Product type:	Medicine
Brand name:	Zelboraf
Generic name:	vemurafenib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-10-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-10-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-11-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-11-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	11-02-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-05-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-06-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-02-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-02-2017
Application type:	Amendment
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	EUCTR2014-002480-15-NL
CCMO	NL48639.031.14