A phase III, randomised, open-label study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma (MEK116513)

Published: 29-05-2012
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Primary: superiority of dabrafenib and trametinib combination therapy over vemurafenib monotherapy with respect to overall survival for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma.Secondary: progression free...

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

Summary

ID

NL-OMON46883

Source
ToetsingOnline

Brief title
MEK116513

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma of the skin

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: dabrafenib, melanoma, trametinib, vemurafenib

Outcome measures

Primary outcome

Overall survival.

Secondary outcome

Progression free survival, overall response rate, duration of response, safety,

tolerability.

Study description

Background summary

Cutaneous melanoma is the most aggressive form of skin cancers. The standard of care (dacarbazine [DTIC]) is not optimal, since the median progression-free survival is approximately 2 months, and the median overall survival is approximately 7 months.
Recently ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen, and the BRAF-inhibitor vemurafenib, which have demonstrated a significant survival benefit, have obtained regulatory approval for unresectable or metastatic melanoma.
Severe toxicities and the lack of a validated biomarker for patient selection

may restrict the use of ipilimumab while the onset of resistance limits the efficacy of vemurafenib. The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers. This pathway can be activated by alterations in specific proteins, including BRAF (via MEK 1-2). BRAF mutations have been identified at a high frequency in specific cancers, including approximately up to 60% of melanoma. The frequency of this activating mutation and the pathway addiction to which it leads makes mutated BRAF an extremely attractive target. GSK2118436 (dabrafenib) is a potent and selective inhibitor of BRAF kinase activity and GSK1120212 (trametinib) is a potent and highly selective inhibitor of MEK1/MEK2 activation and kinase activity. Because both BRAF and MEK are in the same pathway, and MEK is a substrate of activated BRAF, inhibiting both proteins simultaneously rather than individually could provide more effective pathway inhibition. Data generated in animal models with combinations of BRAF and MEK inhibitors suggest enhanced effects on efficacy and less potential for proliferative skin lesions as compared to treatment with a BRAF inhibitor alone. Emerging data from a Phase I/II study suggest that the combination has an acceptable safety profile and increased activity over monotherapy. This is the reason to compare the effects of the combination with those of vemurafenib.

Study objective

Primary: superiority of dabrafenib and trametinib combination therapy over vemurafenib monotherapy with respect to overall survival for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma.
Secondary: progression free survival, overall response rate, duration of response, safety, tolerability.

Study design

Open label, randomized, Phase III study comparing dabrafenib (150 mg bid) and trametinib (2 mg once daily) combination therapy to vemurafenib (960 mg bid) monotherapy. Subjects will be screened for BRAF mutation V600 E/K. Only BRAF mutation positive patients will be eligible.
Treatment until disease progression or severe toxicity. Follow-up for survival.
Approx. 700 patients.
IDMC.

Intervention

Treatment with dabrafenib plus trametinib or vemurafenib.

Study burden and risks

Risk: adverse events of study treatment.
Burden: Most tests/procedures would be performed during regular care as well.

Hardly any extra visits (every 4, thereafter 8-12 weeks).
Extra tests/procedures: approx. 10-20 ml blood extra per occasion (extra safety tests, biomarkers), echocardiogram week 4 and every 12 weeks (plus screening) and ECG week 2, 4, 8 and every 12 weeks (plus screening) , ophthalmic investigation screening and week 4, quality of life questionnaire 1st year week 1 and every 8 weeks, thereafter every 12 weeks.
Optional substudies:
- pharmacogentics (10 ml blood)
- biopsy in case of skin lesions
- remaining (or fresh) tissue for future biomarker research related to the development of GSK2118436 and/or melanoma)
- Biopsy at progression.

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

• Subjects with histologically confirmed advanced or metastatic melanoma
• BRAF V600 E/K mutation positive.
• Measurable disease.
• 18 years and above.
• ECOG Performance Status 0-1.
• Females of childbearing potential: adequate method of contraception.

Exclusion criteria

• Previous treatment for metastatic melanoma, including treatment with BRAF or MEK inhibitor.
• Prior systemic anti-cancer treatment for Stage IIIC or Stage IV melanoma.
• Brain metastases (exceptions see protocol page 29).
• Cardiovascular risk (see protocol page 30 for details).
• A history or current evidence/risk of retinal vein occlusion or central serous retinopathy.
• Pregnancy or breastfeeding

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-09-2012
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mekinist
Generic name:	trametinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tafinlar
Generic name:	dabrafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zelboraf
Generic name:	vemurafenib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-05-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	02-08-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	02-11-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO
Date: 12-12-2012

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 28-12-2012

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 08-01-2013

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 22-03-2013

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 10-04-2013

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 07-06-2013

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 02-08-2013

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 02-09-2013

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 18-10-2013

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 29-10-2013

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 30-10-2013

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 24-01-2014

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 10-02-2014

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 19-02-2014

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 22-05-2014

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 29-07-2014

Application type: Amendment

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Approved WMO
Date: 19-09-2014

Application type: Amendment

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Approved WMO
Date: 08-10-2014

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 17-06-2015

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 11-08-2015

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 09-12-2015

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 27-01-2016

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 09-02-2016

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 19-07-2016

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Date: 31-08-2016

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Date: 13-03-2017

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Date: 27-03-2017

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Date: 26-09-2017

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Date: 09-10-2017

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Date: 10-10-2017

Application type: Amendment

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Date: 17-10-2017

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 07-03-2018

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Date: 04-06-2018

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Date: 31-07-2018

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 16-08-2018

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 23-10-2018

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	24-10-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	31-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	14-03-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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
Other	clinicaltrials.gov; registratienummer n.n.b.
EudraCT	EUCTR2011□006088□23-NL
CCMO	NL40606.058.12