

A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma (MEK115306)

Published: 13-04-2012

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Primary: superiority of dabrafenib and trametinib combination therapy over dabrafenib and trametinib-placebo (dabrafenib monotherapy) with respect to progression-free survival (PFS) for subjects with advanced/metastatic BRAF V600E/K mutation-...

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

Summary

ID

NL-OMON47344

Source

ToetsingOnline

Brief title

MEK115306

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: BRAF, dabrafenib, melanoma, trametinib

Outcome measures

Primary outcome

Progression free survival.

Secondary outcome

Overall survival, overall response rate, duration of response, safety, tolerability, PK.

Study description

Background summary

Cutaneous melanoma is the most aggressive form of skin cancers. The current 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. The need for novel agents for this disease is therefore evident.

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 explore the effects of the combination in a phase III study.

Study objective

Primary: superiority of dabrafenib and trametinib combination therapy over dabrafenib and trametinib-placebo (dabrafenib monotherapy) with respect to progression-free survival (PFS) for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma.

Secondary: overall survival, overall response rate, duration of response, safety, tolerability, PK.

Study design

Double-blinded, randomized, Phase III study comparing dabrafenib (150 mg bid) and trametinib (2 mg once daily) combination therapy to dabrafenib (150 mg bid) administered with a trametinib placebo (dabrafenib 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.

In case of discontinuation of dabrafenib for safety reasons: option to proceed with trametinib/placebo.

Approx. 340 patients.

IDMC.

Intervention

Treatment with dabrafenib plus trametinib or dabrafenib plus a placebo.

Study burden and risks

Risk: adverse events of study treatment.

Burden: Most tests/procedures would be performed during regular care as well.

Visits every 4 weeks. 3-monthly phone calls.

Extra tests/procedures: approx. 10-20 ml blood extra per occasion (extra safety

tests, PK, biomarkers), echocardiogram and ECG 3 monthly, ophthalmic examination at screening and after 4 weeks, MRI brain at screening, quality of life questionnaire 1st year every 8 weeks, thereafter every 12 weeks.

Optional substudies:

- pharmacogenetics (10 ml blood)
- biopsy in case of skin lesions
- biopsy after treatment.

Contacts

Public

Novartis

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Scientific

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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 26).
- * Cardiovascular risk (see protocol page 26 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:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	16-07-2012
Enrollment:	15
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

Ethics review

Approved WMO	
Date:	13-04-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO	
Date:	28-06-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO	
Date:	31-07-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO	
Date:	23-08-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO	
Date:	12-11-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO	
Date:	08-01-2013

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	21-02-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	13-03-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	22-03-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	13-06-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	13-08-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	29-08-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	18-10-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO	
Date:	18-12-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	24-02-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	25-11-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	03-12-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	16-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	17-06-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	22-06-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	29-01-2016
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	10-03-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	27-07-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	12-08-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	06-10-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	13-10-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	15-12-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	16-12-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	12-09-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	14-09-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	12-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	09-04-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	12-04-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	30-05-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	15-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	31-07-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date: 09-08-2018

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
Other	clinicaltrials.gov; registratienummer NCT01584648
EudraCT	EUCTR2011-006087-49-NL
CCMO	NL40285.031.12