COMBI-AD: A phase III randomized double blind study of dabrafenib (GSK2118436) in COMBInation with trametinib (GSK1120212) versus two placebos in the ADjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection (BRF115532)

Published: 19-12-2012
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Primary: efficacy of dabrafenib and trametinib combination therapy compared to placebo with respect to relapse-free survival in patients with completely resected, histologically confirmed, BRAF V600E/K high risk, stage III cutaneous melanoma....

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

Summary

ID

NL-OMON56172

Source
ToetsingOnline

Brief title
BRF115532 COMBI-AD

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: adjuvant, dabrafenib, melanoma, trametinib

Outcome measures

Primary outcome

Relapse-free survival.

Secondary outcome

Overall survival, distant metastasis-free survival, freedom from relapse,

safety, tolerability.

Study description

Background summary

Cutaneous melanoma is the most aggressive form of all skin cancers. Its incidence is continuing to rise. Surgical resection is the treatment of choice for localized melanoma and frequently results in cures for early stage (I and II) disease, with a 90% 10-year survival rate for stage I disease. However, patients with lymph node involvement >=1mm are at high risk of both relapse after definitive surgery. Approximately half of these patients will ultimately die of metastatic. Although high-dose interferon is currently the only approved therapy for the adjuvant treatment of melanoma it is not widely accepted as the standard of care due to a questionable survival benefit and a high incidence of serious toxicities. Thus there is a need for effective adjuvant therapy for these high-risk patients.
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.
Although the role of the MAP kinase pathway has not yet been studied in early melanoma, there is adequate scientific rationale and data to expect that the combination of dabrafenib and trametinib will provide similar responses on V600 mutant cells in the adjuvant setting as for more advanced disease. BRAF mutations are present in primary lesions, and are preserved in corresponding metastatic lesions. The combination of dabrafenib with trametinib in the adjuvant setting is further supported by in vitro and in vivo preclinical data.
This phase III study is designed to evaluate the efficacy of dabrafenib and trametinib combination therapy compared to two placebos with respect to relapse-free survival in patients with completely resected, histologically confirmed, BRAF V600E/K high risk, stage III cutaneous melanoma.

Study objective

Primary: efficacy of dabrafenib and trametinib combination therapy compared to placebo with respect to relapse-free survival in patients with completely resected, histologically confirmed, BRAF V600E/K high risk, stage III cutaneous melanoma.
Secondary: overall survival, distant metastasis-free survival, freedom from relapse, safety, tolerability.

Study design

Double-blind, randomized phase III study comparing (1:1) dabrafenib (150 mg bid) and trametinib (2 mg once daily) combination therapy to placebo (placebos to dabrafenib and trametinib. Subjects will be screened for BRAF mutation V600 E/K. Only BRAF mutation positive patients will be eligible.
Treatment for 12 months or until disease progression or severe toxicity (which ever comes first). Follow-up until progression and thereafter for survival.
Planned study duration (incl. survival follow-up) approx. 5 years.
Approx. 850 patients.

Intervention

Treatment with dabrafenib plus trametinib or placebo.

Study burden and risks

Risk: adverse events of study treatment.
Burden: Monthly visits in 1st, every 3 months in 2nd year and every 6 months thereafter until progression. After progression follow-up for survival (may be by phone).
Tests etc. until progression:
Physical examination every visit (3x incl. rectal examination), eye examination 5x.
Blood tests 13x (approx. 15 ml/occasion plus 5x 15 ml extra for biomarkers).
CT/MRI scan 1st year 5x, 2nd year every 3 months, thereafter every 6 months.
ECG 6x.
Echocardiography 6x.
Tumor biopsy at recurrence.
Questionnaire quality of life 1st year 5x, thereafter every visit/contact (also during survival follow-up).
Only females: PAP-smear 3x, pregnancy test 5x.
Optional substudies:
- pharmacogentic (6 ml blood).
- biopsy in case of skin lesions or new tumor.

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)

Inclusion criteria

• Subjects with histologically confirmed completely resected, BRAF V600E/K high risk, stage III cutaneous melanoma
• Surgically rendered free of disease no more than 12 weeks before randomization.
• 18 years and above.
• ECOG Performance Status 0-1.
• Females of childbearing potential: adequate method of contraception.

Exclusion criteria

• Known mucosal or ocular melanoma or the presence of unresectable in-transit metastases.
• Evidence of distant metastatic disease.
• Prior anti-cancer treatment incl. radiotherapy for melanoma.Prior surgery for melanoma is allowed.
• History of another malignancy including melanoma or a concurrent malignancy. See protocol page 33 for details and exceptions.
• A history or evidence of cardiovascular risk (see protocol page 33 for details).
• A history or current evidence/risk of retinal vein occlusion or central serous retinopathy (see protocol page 34 for details).
• History of interstitial lung disease or pneumonitis.
• 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:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-11-2013
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	dabrafenib
Generic name:	dabrafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	trametinib
Generic name:	trametinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-12-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-05-2013
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-06-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-06-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-07-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-11-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-06-2014
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-04-2016
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-08-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-08-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-12-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-01-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-06-2018
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-11-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-02-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-08-2021
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-01-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-02-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2012□001266□15-NL
CCMO	NL41778.042.12