Phase II, Open-label, Study in Subjects with BRAF V600E - Mutated Rare Cancers with Several Histologies to Investigate the Clinical Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib (BRF117019)

Published: 11-03-2014
Last updated: 20-04-2024

Primary: efficacy of dabrafenib and trametinib combination therapy compared to placebo with respect to overall response rate in subjects with rare BRAF V600E mutated solid tumors or hematologic malignancies.Secondary: duration of response,...

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

Summary

ID

NL-OMON50511

Source
ToetsingOnline

Brief title
BRF117019

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
various rare malignant tumors

Research involving
Human

Sponsors and support

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

Intervention

Keyword: dabrafenib, rare, trametinib, tumors

Outcome measures

Primary outcome

Response.

Secondary outcome

Survival, adverse effects.

Study description

Background summary

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 phase II study is designed to evaluate the efficacy (response) of dabrafenib and trametinib combination in subjects with rare BRAF V600E mutated

solid tumors or hematologic malignancies for which no standard therapy exists. It concerns the following malignancies: Anaplastic Thyroid Cancer, Biliary Tract Cancer, Gastrointestinal Stromal Tumor, Glioma, Germ Cell Tumor, Adenocarcinoma of the Small Intestine, Hairy Cell Leukemia, Multiple Myeloma.

Study objective

Primary: efficacy of dabrafenib and trametinib combination therapy compared to placebo with respect to overall response rate in subjects with rare BRAF V600E mutated solid tumors or hematologic malignancies.
Secondary: duration of response, progression free survival, overall survival, safety.

Study design

Phase II open-label, non-comparative study. Treatment with dabrafenib (150 mg bid) and trametinib (2 mg once daily) combination therapy
Subjects will be screened for BRAF mutation V600E. Only BRAF mutation positive patients will be eligible.
Treatment until disease progression or severe toxicity (which ever comes first). Follow-up until progression and thereafter for survival.
Data monitoring committee with some external members.
Approx. 225 patients.

Intervention

Treatment with dabrafenib plus trametinib.

Study burden and risks

Risk: adverse events of study treatment.
Burden: Visits every 4 weeks until progression. After progression follow-up for survival (may be by phone).
Tests etc. until progression:
Brief physical examination (complete PE at start and end of treatment) and skin examination every 4 weeks (up to 6 months after progression). Eye examination twice (if needed more frequently).
Blood tests every 4 weeks (approx. 15 ml/occasion).
Pregnancy test every 8-12 weeks.
Tumor evaluation (scan(s), echo, bone marrow etc.) every 8-12 weeks.
ECG every 4 weeks.
Echocardiography week 4 and every 12 weeks.
Tumor or bone marrow biopsy treatment day 1, 15, end (optional in some tumor types).
Questionnaire quality of life every 4 weeks.
Optional substudy: pharmacogentic research (6 ml blood), tumor biopsies before

during and at the end of treatment (plus 5 ml blood per occasion).

Contacts

Public
Novartis

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Scientific
Novartis

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Males and females, 18 years and above.
• BRAF mutation positive tumor.
• ECOG Performance Status 0-2.
• Advanced disease, no standard treatment options.
• ATC, BTC, GIST, NSGCT/NGGCT, ASI: at least 1 measurable lesion.
• Females of childbearing potential: adequate method of contraception.,
Histology-specific criteria, see protocol:
• Anaplastic Thyroid Cancer: page 61.
• Biliary Tract Cancer: page 61.

• Gastrointestinal Stromal Tumors: page 61.
• WHO Grade 1 and 2 Glioma: page 61.
• WHO Grade 3 and 4 Glioma: page 62.
• Germ Cell Tumors: page 62.
• Adenocarcinoma of the Small Intestine: page 63.
• Hairy Cell Leukemia: page 63.
• Multiple Myeloma: page 64.

Exclusion criteria

• Prior treatment with BRAF and/or MEK inhibitor.
• Anti-cancer therapy within 21 days (or within 42 days if prior nitrosourea or mitomycin C containing therapy) prior to enrollment and/or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to enrollment.
• Chemotherapy or biologic therapy within 14 days prior to enrolment without evidence of delayed toxicity.
• Investigational drug(s) within 30 days or 5 half-lives, whichever is longer, prior to enrollment.
• Prior radiotherapy treatment and/or major surgery less than 14 days prior to enrolment. Exceptions: see protocol page 51.
• History of interstitial lung disease or pneumonitis.
• Neurological involvement, see protocol page 52-53 for details.
• A history of retinal vein occlusion.
• A history or evidence of cardiovascular risk, see protocol page 53-54 for details.
• Pregnancy or breastfeeding, Histology-specific criteria, see protocol:
• Anaplastic Thyroid Cancer: page 67.
• Biliary Tract Cancer: page 67.
• WHO Grade 1 and 2 Glioma: page 67.
• WHO Grade 3 and 4 Glioma: page 67.

Study design

Design

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

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-02-2015
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mekinist
Generic name:	Trametinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tafinlar
Generic name:	Dabrafenib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	11-03-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	11-11-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	06-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	17-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-04-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-08-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-03-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-03-2016
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:	29-03-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-05-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-09-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-09-2017
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:	15-03-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	30-03-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	13-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	24-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	29-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	06-09-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	06-11-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-07-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-08-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-12-2019

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-01-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-02-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-03-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-07-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-08-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-10-2020
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	EUCTR2013-001705-87-NL
CCMO	NL46478.031.14
Other	www.gskclinicalstudyregister.com; registratienummer 117019