BRIM 3: A Randomized, Open-label, Controlled, Multicenter, Phase III Study in Previously Untreated Patients With Unresectable Stage IIIC or Stage IV Melanoma with V600E BRAF Mutation Receiving Vemurafenib (RO5185426) or Dacarbazine.

Published: 13-11-2009
Last updated: 04-05-2024

Primary objective:To evaluate efficacy of RO5185426 as a monotherapy compared to dacarbazine in terms of progression-free survival (PFS) and overall survival (OS) in previously untreated patients with advanced melanoma harbouring the BRAF V600E...

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

Summary

ID

NL-OMON39219

Source
ToetsingOnline

Brief title
BRIM 3

Condition

- Skin neoplasms malignant and unspecified

Synonym
(metastatic) melanoma, malignant birthmarks

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: pharmaceutische industrie

Intervention

Keyword: Melanoma, Unresectable stage, Untreated patients

Outcome measures

Primary outcome

The co-primary efficacy endpoints are progression-free survival and overall survival.

PFS and OS are defined according to the RECIST 1.1 criteria, see page 70/71 of the protocol.

Secondary outcome

Secondary objective:

• To further assess efficacy of RO5185426 compared to dacarbazine based on best overall response rate (BORR), time to response, duration of response, and time to treatment failure

• To evaluate the tolerability and safety profile of RO5185426 using the NCI CTCAE (version 4.0)

• To further characterize the pharmacokinetic (PK) profile of RO5185426

• To contribute to the validation of the Roche Companion Diagnostic (CoDx) cobas® 4800 BRAF V600E test for the detection of BRAF mutations in DNA extracted from formalin-fixed paraffinembedded tumour (FFPET) samples

Definitions according to RECIST 1.1, as mentioned starting on page 71 of the

protocol,

Study description

Background summary

There are only a limited number of treatments available for metastatic melanoma, and the response to available treatments to date has been extremely poor. In the EU, the only medicinal product approved in the previously untreated metastatic melanoma patients is dacarbazine, which produces 10% to 20% response rates with limited durable responses. Dacarbazine is still considered the standard first-line treatment, despite the lack of any evidence for improving overall survival (OS).

The promising level of activity demonstrated with RO5185426 in the early phase in a targeted melanoma patient population, potentially may translate into an OS improvement. In this randomized trial, the hypothesis that treatment with RO5185426 is associated with an improved progression-free or overall survival compared to dacarbazine in patients with melanoma positive for the V600E mutation will be tested.

Study objective

Primary objective:
To evaluate efficacy of RO5185426 as a monotherapy compared to dacarbazine in terms of progression-free survival (PFS) and overall survival (OS) in previously untreated patients with advanced melanoma harbouring the BRAF V600E mutation

Study design

A randomized, open-label, multi-center, active treatment controlled, Phase III trial that will evaluate the efficacy and safety of vemurafenib (RO5185426) compared to dacarbazine in previously untreated patients with histologically confirmed metastatic melanoma (unresectable Stage IIIC or Stage IV) harboring the BRAF V600E mutation.

Data from this study are being monitored by a Data Safety Monitoring Board (DSMB). If recommended by the DSMO, patients in Arm B (control, receiving dacarbazine, may crossover to Arm A (experimental) to receive RO5185426.

Patients will be randomized to either:

• Experimental Arm A: oral RO5185426 administered twice (b.i.d.) daily at a dose of 960 mg
• Control Arm B: Dacarbazine administered intravenously 1000 mg/m2 on Day 1 every 3 weeks (3 week cycle)

Randomization to the treatment groups will be done in a 1:1 ratio for RO5185426 arm vs. dacarbazine arm.

Intervention

Regime investigational product: Patients receive oral RO5185426 of 960 mg b.i.d. daily
Regime comparator: Dacarbazine administered intravenously 1000 mg/m2 up to 60 minutes on Day 1 of every 3 weeks

Study burden and risks

RO5185426 SIDE EFFECTS
In a study with healthy volunteers, the most common side effects: Headache, dizziness/lightheadedness, itchy rash, drowsiness, decreased white cell counts, and nausea.

In a study with cancer patients:
At least 30% of patients: Fatigue, nausea, diarrhea, rash, itching, hair loss, sensitivity to sunlight, sunburn, dry skin, joint pain, papilloma (bening skin growth), hyperkeratosis (thickening of the outer layer of the skin).

In 25% of patients: developing tumors of the skin (cutaneous squamous cell carcinoma).

At least 10% of patients: Scaly skin, dry skin, hand & foor skin reaction tingling or burning feelings in hands and feet), loss of appetite and weight loss, headache, change in sense of taste.

Other less frequent (occurring in < 10% of patients) side effects:
Basal cell carcinoma (curable cancer of the skin) , acute renal failure (kidneys stop working suddenly), arthritis (joint inflammation), retinal vein occlusion (blockage of blood flow to part of the eye), cellulitis (inflammation/infection of skin), peripheral neuropathy (problem with the nerves that can produce pain, loss of sensation, or muscle weakness), delirium (confusion), a specific type of arrhythmia (prolongation of the QTc interval on ECG), abnormal liver blood tests (which may indicate that your liver is not working properly), pyrexia (fever), tender red skin bumps or lumps.

Other risks: In another study patients treated with vemurafenib for a malignant skin cancer (melanoma) developed new primary melanoma.

The other less frequent side effects and risks of SCC can be read in more detail in the patient information.

RISKS ASSOCIATED WITH THE USE OF DACARBAZINE
Most Common Side Effects are: Facial flushing, numbness or tingling, loss of appetite, metallic taste in mouth, muscle pain or weakness, nausea, temporary hair loss, and vomiting. Less Common Side Effects are: Diarrhea, rash, hives, difficulty breathing, tightness in the chest, swelling of the mouth face, lips, or tongue, dark urine, fever, chills, sore throat, joint pain, stomach pain, unusual bruising or bleeding, unusual tiredness or weakness, yellowing of skin or eyes, and sensitivity to light.

RISKS OF STUDY PROCEDURES
Skin Biopsy and /or skin tumour removal: Risks include pain, discomfort, soreness, redness, swelling, bleeding, bruising, and/or drainage at the biopsy site, abnormal wound healing, fever, infection, or allergic reaction to the anesthesia used to numb the skin over the biopsy site. ECG: You may have mild irritation, slight redness and itching at the places on your skin where the recording patches are placed. Blood Tests: For most people, needle punctures for blood tests do not cause any serious problems. However, they may cause fainting, bleeding, bruising, discomfort, dizziness, infections and/or pain at the injection site.

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

1. Male or female patients >= 18 years of age
2. Patients with histologically confirmed metastatic melanoma (surgically incurable and unresectable stage IIIC or stage IV, AJCC). Unresectable stage IIIC disease must have confirmation from a surgical oncologist
3. Treatment naïve patients (i.e., NO prior systemic anti-cancer therapy for advanced disease; Stage IIIC and IV). Only prior adjuvant immunotherapy is allowed
4. Patients must have a positive BRAF V600E mutation result determined by a designated laboratory using a Roche CoDx BRAF mutation test prior to administration of study treatment
5. ECOG performance status of 0 or 1
6. Life expectancy > 3 months
7. Measurable disease (by RECIST criteria version 1.1) prior to the administration of study treatment
8. Patients must have recovered from effects of any major surgery or significant traumatic injury at least 14 days before the first dose of study treatment
9. Cutaneous SCC lesions identified at baseline, must be excised. Adequate wound healing is required prior to study entry. Baseline skin exam is required for all patients.
10. Adequate hematologic, renal, and liver function as defined by laboratory values performed within 28 days prior to initiation of dosing
- Absolute neutrophil count (ANC) >= 1.5 x 109/L
- Platelet count >= 100 x 109/L
- Hemoglobin >= 9 g/dL
- Serum creatinine <= 1.5 X ULN
- AST and ALT <= 2.5 X ULN
- Bilirubin <= 1.5 X ULN (for patients with Gilbert*s Syndrome, bilirubin <= 3X ULN)
- Alkaline phosphatase <= 2.5 X ULN (< 5 times ULN for patients with concurrent liver metastases)
11. Negative serum pregnancy test within 10 days prior to commencement of dosing in pre-menopausal women. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for >= 1 year
12. Fertile men and women must use an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician (in accordance with local requirements)

13. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry
14. Before study entry, written informed consent must be obtained from patient prior to performing any study-related procedures

Exclusion criteria

1. Patients with active CNS lesions are excluded (i.e. those with radiographically unstable, symptomatic lesions). However, patients treated with stereotactic therapy or surgery are eligible if patient remains without evidence of disease progression in brain >= 3 months. They must also be off corticosteroid therapy for >= 3 weeks. Whole brain radiotherapy is not allowed with the exception of patients who have had definitive resection or stereotactic therapy of all radiologically detectable parenchymal lesions
2. History of carcinomatous meningitis
3. Regional limb infusion or perfusion therapy
4. Anticipated or ongoing administration of anti-cancer therapies other than those administered in this study
5. Pregnant or lactating women
6. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate RO5185426 absorption. Patients must be able to swallow pills
7. Mean QTc interval >= 450 msec at screening
8. NCI CTCAE Version 4.0 grade 3 hemorrhage within 4 weeks of starting the study treatment
9. Any of the following within the 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, serious cardiac arrhythmia requiring medication, uncontrolled hypertension, cerebrovascular accident or transient ischemic attack, or symptomatic pulmonary embolism
10. Known clinically significant active infection
11. History of allogenic bone marrow transplantation or organ transplantation
12. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, which in the judgment of the investigator would make the patient inappropriate for entry into this study
13. Patients with a previous malignancy within the past 5 years are excluded except for patients with basal or squamous cell carcinoma (SCC) of the skin, melanoma in-situ, and carcinoma in-situ of the cervix. Isolated elevation in PSA in the absence of radiographic evidence of metastatic prostate cancer is allowed
14. Patients who have been previously treated with a BRAF inhibitor
15. Known HIV positivity or AIDS-related illness, or active HBV, and active HCV
16. Patients who have been previously randomized to this trial at another participating site

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2009
Enrollment:	26
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Dacarbazine
Generic name:	-
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	vemurafenib
Generic name:	-
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	13-11-2009
Application type:	First submission

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-01-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-01-2010
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-03-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-08-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-08-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-10-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-11-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	29-03-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	17-11-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	16-03-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	24-10-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	28-02-2013
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:	23-08-2013
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:	24-03-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-08-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-08-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-12-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-03-2015

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-03-2015
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	EUCTR2009-012293-12-NL
ClinicalTrials.gov	NCT01006980
CCMO	NL30253.031.09