An open-label, multicenter study to assess the safety of RO5185426 in patients with metastatic melanoma

Published: 31-01-2011
Last updated: 27-04-2024

Primary: To evaluate the safety and tolerability of RO5185426 inpatients with metastatic melanoma (Stage IV; AJCC) harboringthe BRAF V600 mutationSecondary: To evaluate the efficacy of RO5185426 as objectiveresponse rates (ORRs) determined by the...

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

Summary

ID

NL-OMON39617

Source
ToetsingOnline

Brief title
MO25515

Condition

- Skin neoplasms malignant and unspecified

Synonym
aggressive skin cancer, metastatic melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Roche

Intervention

Keyword: BRAF, Melanoma, RO5185426

Outcome measures

Primary outcome

Primary: To evaluate the safety and tolerability of RO5185426 in

patients with metastatic melanoma (Stage IV; AJCC) harboring

the BRAF V600 mutation

Secondary outcome

Secondary: To evaluate the efficacy of RO5185426 as objective

response rates (ORRs) determined by the investigator (RECIST,

Version 1.1) as allowed by local regulatory requirements.

Study description

Background summary

Patients with metastatic melanoma have few treatment options and prognosis is poor.
Despite many years of clinical research no evidence of survival prolongation has been
established and the prognosis of metastatic melanoma remains poor with a median survival time of only 6 to 9 months from the diagnosis of distant metastases.
There have been many efforts to identify new drug targets for melanoma and BRAF mutations in melanoma have been identified as an important target. RO5185426 is a low molecular weight, orally available, selective inhibitor of the
activated form of the BRAF serine-threonine kinase enzyme, which is commonly found
in malignant melanoma.
Results from phase I and II trials indicate that RO5185426 initiates a good response for patients with metastic melanoma who have the V600E BRAF mutation.
This data suggest that RO5185426 could be an effective treatment option in this patient population.

Study objective

Primary: To evaluate the safety and tolerability of RO5185426 in patients with metastatic melanoma (Stage IV; AJCC) harboring the BRAF V600 mutation
Secondary: To evaluate the efficacy of RO5185426 as objective response rates (ORRs) determined by the investigator (RECIST, Version 1.1) as allowed by local regulatory requirements.

Study design

Open-label, multicenter, multi-national, safety study of RO5185426 in patients with BRAF V600 mutation-positive (identified by the cobas® 4800 BRAF V600 Mutation Test) metastatic melanoma (stage IV; AJCC) who have failed at least one previous systemic treatment for metastatic melanoma and are without satisfactory treatment options.

The trial will consist of a screening period (Day *28 to *1), a treatment phase, and a follow up. Day 1 of study will be defined as the first day a patient receives RO5185426. One cycle of therapy is defined as 28 days of treatment. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

Enrolled patients will receive continuous oral dosing of RO5185426 at 960 mg twice daily (b.i.d) until the development of progressive disease (as per investigator assessment), unacceptable toxicity, consent withdrawal, death, reasons deemed by the treating physician or study termination by the Sponsor. Patients who discontinue from study drug (RO5185426) will attend an end of study visit and a follow-up visit within 28 days after the last dose of RO5185426.

Patients who discontinue study RO5185426 for any reason (i.e. an adverse event [AE], etc.) other than disease progression or withdrawal of consent will continue to be followed until the development of disease progression, withdrawal of consent, lost to follow up or beginning of another anti-cancer therapy. The investigator/designee will collect and document in the electronic case report forms (eCRFs) whether the patient has progressed or not (tumor assessments as per institutional standard of care). The first anti-cancer therapy received by the patient after discontinuation of RO5185426 will also be recorded in the eCRFs.

Intervention

Patients take orally 2x daily 4 tablets RO5185426.

Study burden and risks

The following assessments are done during the study:

Screening/Baseline:
* Informed Consent
* Submission of tumor tissue for the V600 BRAF mutation screening using the cobas® 4800 BRAF
V600 Mutation Test
* Medical history (including demographics)
* Physical exam including height (screening only) and weight
* Dermatology evaluation
* Head & Neck examination (as part of the evaluation for SCC)
* Vital signs (blood pressure, pulse, temperature, respiratory rate)
* ECOG PS
* Hematology (including hemoglobin, hematocrit, Platelet Count, White Blood Cell Count [WBC],
ANC)
* Biochemistry (including glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance,
sodium, potassium, bicarbonate [if routinely performed on venous blood samples], total bilirubin
with fractionation into direct and indirect (if total bilirubin elevated),
alkaline phosphatase, AST
[SGOT], ALT [SGPT], lactate dehydrogenase (LDH)
* Serum pregnancy test (within 7 days prior to commencement of dosing) for women of childbearing
potential.
Tumor assessments including measurable and non-measurable lesions (CT/MRI of brain, chest,
abdomen and pelvis [C/A/P] and bone scan if clinically indicated)
* CT of chest for evaluation of non cutaneous SCC
* Pelvic examinations for women (with special attention to cervix) and anal examinations for all
patients for evaluation of SCC
* 12-lead ECG
* AEs / SAEs
* Concomitant therapy

During Study
* Physical exam at every 28-Day visit
* Dermatology evaluation by a dermatologist (28 days on therapy and every 12 weeks while on
study)
* Head and neck examination (as part of the evaluation for non cutaneous SCC, every 12 weeks

while on study)
* Vital signs (blood pressure, pulse, temperature, respiratory rate) at every 28-Day visit
* ECOG PS at every 28-Day visit
* Hematology (including hemoglobin, hematocrit, platelet count, WBC, ANC) at every 28-Day visit
* Biochemistry (including glucose, BUN, creatinine or creatinine clearance, sodium, potassium,
bicarbonate [if routinely performed on venous blood samples], total bilirubin with fractionation
into direct and indirect (if total bilirubin elevated), alkaline phosphatase, AST [SGOT], ALT
[SGPT] and lactate dehydrogenase (LDH) at every 28-Day visit
* Tumor assessments of both measurable and non-measurable disease (CT/MRI of the brain as
clinically indicated; C/A/P CT/MRI every 8 weeks during the first 16 weeks of treatment and as
per institutional standard of care thereafter but at a minimum of every 16 weeks).
* CT of chest for evaluation of non cutaneous SCC (once every 6 months during treatment period)
* 12-lead ECG (during the study as clinically indicated)
* Concomitant therapy and AEs (including SAEs) throughout the study
* RO5185426 administration throughout the study

End of Study Visit
* Physical exam
* Vital signs (blood pressure, pulse, temperature, respiratory rate)
* ECOG PS
* Head and neck examination for evaluation of non cutaneous SCC
* Dermatology evaluation by a dermatologist for evaluation of cutaneous SCC
* Hematology (including hemoglobin, hematocrit, platelet count, WBC, ANC)
* Biochemistry (including glucose, BUN, creatinine or creatinine clearance, sodium, potassium,
bicarbonate [if routinely performed on venous blood samples], total bilirubin with fractionation
into direct and indirect (if total bilirubin elevated), alkaline phosphatase, AST [SGOT], ALT
[SGPT] and lactate dehydrogenase (LDH)
* Tumor assessments (CT/MRI)
* 12-lead ECG (if clinically indicated)
* Concomitant therapy and AEs (including SAEs)
* New anti-cancer therapy

Follow up Visit
* Head and neck examination for evaluation of non cutaneous SCC
* Dermatology evaluation by a dermatologist for evaluation of cutaneous SCC

* CT of chest for evaluation of non cutaneous SCC must be performed within 3-6 months following
discontinuation of study drug
* Pelvic examinations for women (with special attention to cervix) and anal examinations for all
patients for evaluation of SCC
* 12-lead ECG (if clinically indicated)
* Concomitant therapy and AEs (including SAEs)
* New anti-cancer therapy

In cancer patients, the most common side effects that have occurred in at least 10% of patients and were thought to be related to the study drug are:
* Fatigue
* Nausea
* Diarrhea
* Increased amounts of bilirubin in the blood (a finding that may occur with injury or damage to liver or red blood cells)
* Increased amounts of alanine aminotransferase in the blood (a finding that may occur with injury or damage to liver cells)
* Rash
* Cutaneous squamous cell carcinoma (SCC)
* Scaly skin
* Itching
* Hair loss
* Sensitivity to light
* Sunburn
* Dry skin
* Joint or muscle pain
* Tingling or burning feelings in hands and feet
* Loss of appetite and weight loss
* Headache
* Change in sense of taste

In addition, the following serious but rare adverse side effects have been reported in cancer patients.
* Basal cell carcinoma (a curable cancer of the skin)
* Hand & foot skin reaction (tingling or burning feelings in hands and feet)
* Pancreatitis (inflammation or infection in the pancreas)
* Anterior uveitis (inflammation in the middle layer of the eye)
* Acute renal failure (the kidneys stop working suddenly)
* Dysphagia (difficulty in swallowing)
* Arthritis (joint inflammation)

Also side effects with are currently unknown might occur during the study.

Participation in the study may help patients in the future by giving important

information about RO5185426 and the treatment of metastatic melanoma. Also the medical condition of the patients included in this trial might improve, but this cannot be guaranteed.

Contacts

Public
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446GR
NL
Scientific
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446GR
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In het engels:
A patient may be included if the answer to all of the following statements is "yes".
1. Male or female patients * 18 years of age
2. Patients with histologically confirmed metastatic melanoma (Stage IV, AJCC) with documented BRAF V600 mutation as determined be the cobas® BRAF

V600 Mutation Test prior to administration of RO5185426.
3. Patients with either measurable or non-measurable disease (RECIST Version 1.1).
4. Patients must have progressed during or after at least one prior systemic treatment for metastatic melanoma
5. ECOG PS of 0-2
6. Patients must have recovered from all side effects of their most recent systemic or local treatment for metastatic melanoma
7. Adequate hematologic, renal and liver function as defined by the following laboratory values performed within 7 days prior to first dose of RO5185426:
* ANC * 1.5 x 109/L
* Platelet count * 100 x 109/L
* Hemoglobin * 9 g/dL
* Serum creatinine * 1.5 times ULN or CrCl > 50 mL/hr by Cockroft*Gault formula
* AST and ALT * 2.5 times ULN (*5 times ULN if considered due to tumor)
* Serum Bilirubin * 1.5 times ULN
* Alkaline phosphatase * 2.5 times ULN (* 5 times ULN if considered due to tumor)
8. Negative serum pregnancy test within 7 days prior to commencement of dosing in premenopausal women. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for * 1 year
9. 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. Effective methods of contraception are defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly (for example implants, injectables, combined oral contraception or intra-uterine devices). At the discretion of the investigator, acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance.
CONFIDENTIAL Roche Protocol MO25515 (RO5185426) - Page 40
[Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.]
10. 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
11. Signed informed consent must be obtained prior to performing any study-related procedures (including tumor testing for the V600 BRAF mutation)

Exclusion criteria

1. Evidence of symptomatic CNS lesions as determined by investigator, use of steroids or anti-seizure medications for treatment of brain metastases prior to the first administration of RO5185426. Patients with asymptomatic lesions previously irradiated or surgically resected that are radiologically stable are eligible. Patients with incidentally found brain metastasis that are asymptomatic and for which no treatment is planned are also eligible
2. Patients with a previous malignancy (other than melanoma) within the past 2 years

are excluded except for patients with treated and controlled basal or SCC of the skin or carcinoma in-situ of the cervix. Isolated elevation in PSA in absence of radiographic evidence of metastatic prostate cancer is allowed
3. Concurrent administration of any anti-cancer therapies (e.g. chemotherapy, other targeted therapy, experimental drug, etc) other than those administered in this study
4. Pregnant or lactating women
5. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate absorption. Patients must be able to swallow tablets
6. Any of the following within the 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, hypertension not adequately controlled by current medications
7. History of or presence of clinically significant ventricular or atrial dysrhythmias * Grade 2 (NCI CTCAE Version 4.0)
8. Corrected QT (QTc) interval * 450 msec at baseline
9. Uncontrolled medical illness such as infection requiring treatment with IV antibiotics
10. 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
11. Unwillingness to practise effective birth control
12. Inability to comply with other requirements of the protocol

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-03-2011
Enrollment:	280
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	31-01-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-03-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	31-05-2011
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:	16-01-2012
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:	26-04-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-07-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-10-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-11-2012
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:	15-10-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-11-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-03-2014
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:	02-04-2014
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:	28-08-2014
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:	30-10-2014
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:	02-03-2016
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)

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	EUCTR2010-023526-21-NL

Register	ID
CCMO	NL35202.031.11