A multicentre, open label, randomized Phase II trial of the MEK inhibitor pimasertib or dacarbazine in previously untreated subjects with N-Ras mutated locally advanced or metastatic malignant cutaneous melanoma

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Primary objectiveTo compare the progression-free survival (PFS) of subjects treated with either pimasertib or dacarbazine.Secondary objectivesEfficacy- To compare the objective response of subjects treated with either pimasertib or dacarbazine.- To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON41477

Source
ToetsingOnline

Brief title
EMR 200066-007

Condition

- Metastases

Synonym
maligne, Skin cancer

Research involving

Human

Sponsors and support

Primary sponsor: Merck Serono S.A. Geneva
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Decarbazine, Malignant cutaneous melanoma, N-Ras mutated, Pimasertib

Outcome measures

Primary outcome

PFS, defined as the time from randomization to the first documentation of objective disease progression (according to RECIST v. 1.1) as determined by the investigator, or death, whichever comes first. Death will be considered as an event only if it is reported within 12 weeks after the last tumor assessment without progression.

Secondary outcome

Efficacy

All efficacy endpoints involving RECIST v. 1.1 criteria will be based upon investigator assessment.

- Objective response is defined as complete or partial tumor response according to RECIST v. 1.1 criteria.

- Disease control is defined as complete response, partial response or stable disease for >3 months, according to RECIST v. 1.1 criteria.

- PFS rate at 6 months from the time of randomization based upon objective disease progression (according to RECIST v. 1.1), as defined for PFS above.

- OS defined as the time from randomization to death from any cause.

- OS rate at 12 months from the time of randomization.

- Change in subject-reported QoL (assessed by FACTMelanoma) from baseline assessment to last assessment prior to objective disease progression (according to RECIST v. 1.1).

Safety

- Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths.

- Clinically significant changes in safety related laboratory parameters according to NCI-CTC v 4.0 and abnormal vital signs.

Pharmacokinetics

- Plasma PK parameter estimates of pimasertib.

Pharmacogenetics and Biomarkers

- Gene products and genetic alterations in tumor biopsies

- Predictive markers in plasma

- Potential genetic variations in gDNA obtained from PBMC, associated with differences in PK (i.e., DMET genes) profile of pimasertib.

Study description

Background summary

In human malignancies, activating Ras mutations are common, having been identified in about 30% of cancers. Ras activation through the Raf/MEK/ERK pathway modulates the activity of nuclear factors, which regulate the transcription of genes that are required for proliferation and differentiation. Activating B-Raf mutations occur in a high percentage of malignant melanomas. Selectively pharmaceutical inhibition of MEK has resulted in a decreased proliferation of melanoma cells with Raf muations. Based on this data, MEKs are the targets of great interest for the development of new therapeutics in

the treatment of N-Ras mutated malignant cutaneous melanoma. Pimasertib is being developed for the treatment of cancer. The safety and tolerability, pharmacokinetics, pharmacodynamics and antitumor activity of this compound is under investigation in patients with advanced malignancies.
Preliminary data from preclinical experiments indicate that pimasertib is an active against N-Ras mutated cell lines and a potential medication to inhibit the Raf/MEK/ERH pathway and potentially a positive effect on N-Ras mutated malignant cutaneous melanoma.

Study objective

Primary objective
To compare the progression-free survival (PFS) of subjects treated with either pimasertib or dacarbazine.

Secondary objectives
Efficacy
- To compare the objective response of subjects treated with either pimasertib or dacarbazine.
- To compare the disease control of subjects treated with either pimasertib or dacarbazine.
- To evaluate the overall survival (OS) of subjects treated with either pimasertib or dacarbazine.
- To compare the Quality of Life (via FACTMelanoma) of subjects treated with either pimasertib or dacarbazine.
Safety
- To compare the safety profile of subjects treated with pimasertib or dacarbazine.
Pharmacokinetics
- To assess the pharmacokinetics (PK) of pimasertib in melanoma subjects and to evaluate relationships between exposure and response as well as exposure and adverse events (AEs).
Pharmacogenetics and Biomarkers
- To describe the relationship between basal tumor characteristics (e.g., genotype, gene products) and circulating markers and pimasertib anti-tumor activity.
- To explore genes that are important in the drug metabolizing enzymes and transporters (DMET) of pimasertib and to identify potential genetic variations that may account for differences in PK profile.

Study design

This will be a phase II, multicentre, randomized, controlled pimasertib versus dacarbazine (2 vs. 1), open label trial. The aim of the trial is to confirm the activity of pimasertib in previously untreated subjects with locally advanced or metastatic N-Ras mutated malignant cutaneous melanoma and to quantify it

versus dacarbazine. Secondary aims of the trial are to get a better understanding of the efficacy, safety, pharmacogenomics (PGx) and their relationship with pimasertib exposure. Subjects progressing in the dacarbazine arm will be proposed pimasertib treatment (switch).

For each individual subject the trial will include:
- Up to 35-day screening and baseline evaluation period,
- Trial treatment period consisting of consecutive 21-day cycles of treatment,
- Post-treatment period: 30 ±3 days after the last drug intake.
- Survival follow-up data will be collected every 6 months until the end of the trial.

Intervention

Pimasertib as monotherapy at an oral dose of 60 mg twice daily (BID) continuously.
Dacarbazine 1000 mg per square meter of body surface area intravenously (IV) every 3 weeks.

Treatment will consist of repeated 21-day cycles. Treatment will continue until progression of the disease, unacceptable toxicity, withdrawal of informed consent, or death.

Study burden and risks

See Flowchart of Protocol version 1.0 (15Jun12) on page 65-75.

Summary of procedures:
ECG
Blood sampling
Urine sampling
Questionnaires
Eye tests

Most frequent side effects of pimasertib are: nausea, vomiting and diarrhoea, sores in the mouth and esophagus, which may be painful and cause difficulty swallowing (stomatitis/mucositis), skin changes (including rash, dry skin and acne). Abnormal vision including but not limited to blurry vision or worsening of vision has also been observed frequently. Less frequent: temporary loss of vision.

Contacts

Public

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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. Subjects with measurable, histologically or cytologically confirmed, unresectable locally advanced or metastatic cutaneous melanoma (M1a-c) N-Ras mutated. If N-Ras mutational status is unknown at screening, it must be prospectively defined before inclusion. If N-Ras mutational status is already known before screening, it must be retrospectively confirmed after inclusion by the sponsor.
2. Tumor lesions amenable to biopsy or available tumor tissue as archival samples.
3. Age >= 18 years.
4. Has read and understands the informed consent form and is willing and able to give informed consent. Fully understands requirements of the trial and willing to comply with all trial visits and assessments.
5. Women of childbearing potential must have a negative blood pregnancy test at the screening visit. For the purposes of this trial, women of childbearing potential are defined as: *All female subjects after puberty unless they are post-menopausal for at least two years, are surgically sterile.*
6. Female subjects of childbearing potential and male subjects with female partners of childbearing potential must be willing to avoid pregnancy by using an adequate method of

contraception for 2 weeks prior to, during and four weeks after the last dose of trial medication. Effective contraception is defined as the method of contraception with a failure rate of less than 1% per year. Adequate contraception for females subjects and female partners of male subjects is defined as follows: two barrier methods or one barrier method in combination with an intrauterine device or oral contraception.

Exclusion criteria

1. Has previous systemic treatment for locally advanced or metastatic cutaneous melanoma (excluding adjuvant treatment).
2. Has non-measurable lesions, disease not evaluable by RECIST v. 1.1
3. Has an Eastern Cooperative Oncology Group performance status (ECOG PS) >1.
4. Has bone marrow impairment as evidenced by Hemoglobin < 10.0 g/dL, Neutrophil count <1.5 x 109/L, platelets < 100 x 109/L.
5. Has renal impairment as evidenced by calculated creatinine clearance <60 mL/min (according to the Cockcroft-Gault formula).
6. Has liver function abnormality as defined by total bilirubin > 1.5 x ULN, or AST/ALT >2.5 x ULN, for subjects with liver involvement AST/ALT >5 x ULN.
7. Has significant cardiac conduction abnormalities, including QTc prolongation of >480 ms and/or pacemaker or clinically relevant impaired cardiovascular function (NYHA Class III/IV).
8. Has hypertension uncontrolled by medication
9. Has retinal degenerative disease (hereditary retinal degeneration or age-related macular degeneration), history of uveitis, or history of retinal vein occlusion (RVO) or any eye condition that would be considered a risk factor for RVO (e.g., uncontrolled glaucoma or ocular hypertension).
10. Has known active CNS metastases unless previously radiotherapy treated, stable by CT scan for at least 3 months without evidence of cerebral edema and no requirements for corticosteroids or anticonvulsants.
11. History of difficulty swallowing, malabsorption or other chronic gastro-intestinal disease, or conditions that may hamper compliance and/or absorption of the tested product.
12. Known HIV positivity, active hepatitis C, or active hepatitis B.
13. Has undergone surgical intervention within 28 days from Day 1 of trial drug treatment.
14. Has received extensive prior radiotherapy on more than 30% of bone marrow reserves, or prior bone marrow/stem cell transplantation within 5 years from Day 1 of trial drug treatment.
15. Has history of any other significant medical disease such as major gastric or small bowel surgery, recent drainage of significant volumes of ascites or pleural effusion or has a psychiatric condition that might impair the subject well-being or preclude full participation in the trial.
16. Has known hypersensitivity to dacarbazine.
17. Is a pregnant or nursing female.
18. Participated in another clinical trial within the past 28 days.
19. Has CPK level at baseline NCI CTCAE Grade >=2 (i.e., > 2.5 x ULN),
and/or has a previous history of myositis or rhabdomyolysis.
20. Is suitable for treatment with an approved B-Raf inhibitor or

antihuman
CTLA-4 (CD152) monoclonal antibodies (such as ipilimumab).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-04-2013
Enrollment:	10
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	01-08-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-11-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-02-2013
Application type:	First submission
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:	17-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-11-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-09-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	30-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-07-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-07-2015
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
EudraCT	EUCTR2012-002669-37-NL
CCMO	NL41319.042.12