A Phase I/II, Open Label, Dose Escalation Trial to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of RAF265 (CHIR-265) Administered Orally to Patients with Locally Advanced or Metastatic Melanoma.

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• Determine the MTD of RAF265 when administered orally to patients with locally advanced or metastatic melanoma. (Phase I)• Determine the safetyprofile of RAF265 (phase I and II)• Determine the plasma PK of orally administered RAF265 (phase I and II...

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

Summary

ID

NL-OMON33745

Source
ToetsingOnline

Brief title
Phase I/II trial with RAF265 in locally advanced or metastatic melanoma.

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma, skin cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: melanoma, Phase I/II trial, RAF265

Outcome measures

Primary outcome

- The number of DLTs (phase I)

- Safety profile (frequency and severity of AEs, laboratory-test results, ECG, ECHO, vital signs and weight) of RAF265 administered orally to patients with locally advanced or metastatic melanoma.

- plasma PK levels of orally administered RAF265 (including but not limited to area under the curve (AUC), half-life [t1/2], observed maximum plasma concentration [Cmax], time at which maximum concentration is observed [tmax], and pre-dose plasma concentration [Cmin])

- Best tumor response to treatment according to the RECIST criteria

Secondary outcome

- Progression-free survival

- For each patient with a response to therapy, duration of response will be calculated.

- Relationships between antitumor activity, BRAF, NRAS, c-KIT, p53, CDKN2A and

PTEN mutation status (if analyzed), pharmacodynamic markers, and drug exposure

levels will be explored.

- Response rate at the MTD and/or OBD will be summarized for patients with or

without BRAF mutations.

- K-trans will be summarized for its change from baseline.

Study description

Background summary

Cutaneous malignant melanoma is a highly invasive form of skin cancer. The incidence of malignant melanoma is rapidly increasing throughout the world. Clinical outcome is dependent on the extent of disease at diagnosis with excellent survival rates (approximately 90% at 5 years) described for patients with stage I disease. By contrast, very poor survival rates (ranging from 6.7% to 18% at 5 years) with median survival of 6 to 9 months are reported for those patients with metastatic (stage IV) disease.
The poor survival of patients with metastatic melanoma appears to result from the disease*s chemoinsensitivity.
Recent advances in the understanding of the genetic basis of melanoma have motivated the development of new therapies for this disease. Previous studies implicated mutations in K-Ras and NRAS in the pathogenesis of melanoma. More recently, activating somatic mutations in the BRAF gene have been observed in a wide variety of human tumors, most notably melanoma. Somatic mutations in BRAF have been detected in approximately two-thirds of melanoma tumors and cell lines.
B-Raf is a member of the Ras/Raf/MEK/ERK pathway. This pathway plays a prominent role in controlling several key cellular functions including growth, proliferation, and survival.
These findings suggest that inhibition of the Ras/Raf/MEK/ERK pathway would have therapeutic benefit in melanoma patients. Specifically, the high frequency of B-Raf (V600E) mutations in patients with melanoma has led to the development of new drugs targeting this mutant B-Raf protein. RAF265 is a novel, orally active, small molecule with potent inhibitory activity against mutant B-Raf kinase and additional anti-angiogenic activity through inhibition of vascular endothelial growth factor receptor type 2 (VEGFR-2).

Study objective

• Determine the MTD of RAF265 when administered orally to patients with locally

advanced or metastatic melanoma. (Phase I)
• Determine the safetyprofile of RAF265 (phase I and II)
• Determine the plasma PK of orally administered RAF265 (phase I and II)
• Determine the efficacy of RAF265 (phase II)
•The primary objective of Arm 4 is to confirm the safety and tolerability of the tablet formulation of RAF265 when dosed daily at its MTD, and to confirm that exposure withthe tablet is comparable to that of the liquid formulation under steady-state conditions.

Study design

The study has four treatment arms.
Patients enrolled under the original protocol will be included in Arm 1. This arm was terminated after the pharmacokinetic data from these first two patients showed that RAF265 has a long plasma t1/2.
Arm 2 of the study will comprise two phases: a dose escalation phase and an MTD or OBD expansion phase. In the Netherlands we will participate in the MTD or OBD expansion phase (or Phase II).
Once the MTD has been defined, an expanded evaluation of safety, PK, pharmacodynamics, and tumor response at the MTD or OBD for RAF265 will be conducted in approximately 40 to 80 patients.
Patients in the dose expansion phase will be stratified into two groups, depending on the
tumor*s BRAF mutational status determined from an archival tumor if available or from
tumor biopsy done at baseline if no archived tissues is available. The two groups are mutant BRAF group and wild-type BRAF group.
Arm 3 of the study will comprise two phases: a dose escalation phase and an MTD or OBD expansion phase. Patients in Arm 3 will receive a single dose of RAF265 once weekly. Arm 3 of the study may undergo only limited evaluation unless the dosing regimen evaluated in Arm 2 is not well tolerated at potentially therapeutic doses.
Arm 4 will commence once the MTD is determined in Arm 2. Arm 4 will confirm the safety and tolerability of the RAF265 tablets.

Intervention

In this study RAF265 will be administered orally to patients with locally advanced or metastatic melanoma.

Study burden and risks

Possible side effects of RAF265.
There will be additional visits, blood samples, ECG assessments, PET scans, biopsies, echo assessments during treatment. These additional assessments are

needed for reasons of safety and monitoring efficacy.

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

Age > 18 years;Histologically confirmed diagnosis of locally advanced or metastatic melanoma (for cutaneous melanoma American Joint Committee on Cancer (AJCC) Stage IIIb to IV, pathologic Stage III and IV for noncutaneous melanoma), (see Appendix 1 for the AJCC Staging System for Cutaneous Melanoma).;Must have either archival tumor tissue or tumor that can be biopsied in order to determine whether it contains mutated or wild-type BRAF.;Evidence of measurable disease.;ECOG 0-1

Exclusion criteria

Previous therapy with the following molecularly-targeted agents: MEK inhibitors VEGF or VEGFR inhibitors, RAF inhibitors;Patients with a history of primary central nervous system tumors or brain metastases or who have signs/symptoms attributable to brain metastases and have not been assessed with radiologic imaging to rule out the presence of brain metastases.;Clinically significant cardiac disease including congestive heart failure.;Previous or concurrent malignancy except adequately treated basal cell or squamous cell skin cancer, in situ carcinoma of the cervix, or other solid tumor treated curatively, and without evidence of recurrence for at least 3 years prior to study entry.;Chronic anticoagulation therapy with full strength acetylsalicylic acid, warfarin, sodium, or heparin;History of thromboembolic or cerebrovascular events within the last 12 months, including transient ischemic attack, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism.;Prior acute or chronic pancreatitis of any etiology.;Prior intra or extrahepatic biliary obstruction within the previous 12 months, or history of malignant obstruction requiring a biliary stent, unless stably treated with no prior obstruction or blockage of the stent.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-06-2009
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	06-04-2009
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-05-2009
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-07-2009
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-05-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-06-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-08-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-09-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2007-005367-10-NL
ClinicalTrials.gov	NCT00304525
CCMO	NL25147.091.09