A phase Ib/II, open-label, multicenter study of AEB071 and MEK162 in adult patients with metastatic uveal melanoma

Published: 19-06-2013
Last updated: 24-04-2024

Phase Ib: Estimate the MTD and the RP2D of the combination of AEB071 and MEK162 in patients with metastatic uveal melanoma. And to assess the preliminary anti-tumor activity of the combination of AEB071 and MEK162. To characterize the PK profiels of...

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

Summary

ID

NL-OMON40465

Source
ToetsingOnline

Brief title
Ph Ib/II study of AEB071+MEK162 in patients with metastatic uveal melanoma

Condition

- Ocular neoplasms
- Ocular neoplasms

Synonym
Uveal melanoma; Cancer of the eye

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AEB071, MEK162, phase Ib/II, uveal melanoma

Outcome measures

Primary outcome

Phase 1b: Incidence of Dose Limiting Toxicities during the first cycle

Phase II: Progression Free Survival (PFS)

Secondary outcome

Phase Ib/II: Adeverse events and serious adverse events, changes in laboratory values, and electrocardiograms. Dose interruptions, reductions and dose intensity.

Phase 1b/11: Disease control Rate (DCR: CR(complete resonse)+PR (partial response) +SD (stable disease); Progression Free Survival (PFS); OS(overall survival); ORR (Overall Response Rate)

Phase 1b: Concentration-time profiles of AEB071 and MEK162, PK parameters, including but not limited to AUC0-8h, Ctrough, Cmax, Tmax, accumulation ratio (Racc)

Study description

Background summary

No standard of care excist for patients with metastatic uveal melanoma and, due to lack of available therapies, outcome for these patients is extremely poor.

AEB071 is able to attach to a protein called Protein Kinase C (PKC) and stop it from working. PKC is involved in the regulation of healthy cells and if PKC becomes too active it can cause tumor cell growth and help the tumor cells survive. In uveal melanoma some genes are changed and these genes make proteins that increase the activity of PKC. Giving AEB071 to patients is expected to

reduce the increased activity of PKC, but this is not guaranteed.
MEK162 is a type of medicine that works by stopping a protein called MEK from working. This protein is one of a number of proteins working together in the cell (together they are called a signaling pathway) to cause changes in the cell. If the signaling pathway is too active it can cause certain types of cancers. Although not directly causing uveal melanoma, the signaling pathway may also be activated by PKC. Adding MEK162 may help reduce the activity of the signaling pathway. The combination of the two medicines may slow or stop tumor growth and may make tumors shrink, but this is not guaranteed. Animal studies have shown that the combination of the two medicines leads to a greater decrease in tumor growth than either drug given alone. The two drugs together have not been tested before in patients with uveal melanoma and it is not known whether they will be effective on the tumor or how effective they may be

The startdose of AEB071 is 400mg BID and of MEK162 30mg BID. Higher dosis could be necessary to achieve anti-tumor activity. More details are found in paragraph 1 and 2 of the protocol.

Study objective

Phase Ib: Estimate the MTD and the RP2D of the combination of AEB071 and MEK162 in patients with metastatic uveal melanoma. And to assess the preliminary anti-tumor activity of the combination of AEB071 and MEK162. To characterize the PK profiels of AEB071 and MEK162, as well as evaluate their active metabolites
Phase II: Compare the preliminiary evidence for anti-tumor activity and clinical benefit (measured as progression free survival) at the RP2D of AEB071 and MEK162 and at 45mg BID of single-agent MEK162. And to evaluate the preliminiary anti-tumor activity at the RP2D for AEB071 and MEK162 and at 45 mg BID of MEK162 alone.
For both phase 1b and phase II an objective is to further characterize the safety and tolerability of the combination of AEB071 and MEK162, including actue and chronic toxicities.

Study design

Phase Ib: Open label, multicenter, single arm, phase I dose finding part (Bayesian) and escalation study
Phase II: Randomized open label, multicenter, two arms, phase II study

Intervention

Phase Ib: treatmet with AEB071 and MEK162
Phase II: treatment with AEB071 and MEK162 or with MEK162 only

Study burden and risks

Toxicities of the treatment with AEB071 and MEK162
Tumorbiopsies.
Exposure to radiation, CTscan (or X-ray, MRI or PETscan). Frequent visits and blooddrawn.
See attachment C of the patientinformation for an overview of all the procedures during the visits. The side effects are found in attachment D of the patientinformation.
There is no guarentee that participation of this trial has direct benefit for the patient. Obtained results could help devolpment in the future.
The burden on the patient is as expected in a phase Ib and II study.

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. Male or female patients >=18 years of age
2. Uveal (ocular) melanoma with biopsy-confirmed metastatic disease
3. Consent to a new tumor biopsy at baseline, Cycle 1 Day 15 (C1D15), and at disease progression
4. The presence of measurable disease according RECIST v1.1
5. WHO performance status of <=1

Exclusion criteria

1. Any active metastatic CNS lesion
2. History of prior or current second malignancy (except adequately treated carcinoma of the cervix or localized basal cell carcinoma of the skin, or any other curatively treated malignancy that has not been treated or recurred in the past 3 years).
3. History or current evidence of retinal vein occlusion (RVO) in the contralateral eye, as assessed by ophthamologic examination at baseline or current risk factors for RVO.
4. Impaired cardiac function ro clinically significant cardiac disease; e.g. , LVEF < 50% as determined by MUGA scan or TTE
5. Serum creatinine of >1.5x ULN
6.Treatment with strong inducers or inhibitors (medications and herbal supplements) of cytochrome P450 3A4/5 (CYP3A4/5) or CYP3A4/5 substrates with a QT prolongation risk that cannot be discontinued at least 7 half lives (or if the half-life is unkonw, 14 days) prior to study drug treatment.
7.Prior exposure to a MEK or PKC inhibitor (i.e. patients treated in the Phase I will not be eligible for the Phase II)

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped

Start date (anticipated):	17-09-2013
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.a.
Generic name:	sotrastaurine

Ethics review

Approved WMO Date:	19-06-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-08-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-09-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	30-10-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Approved WMO Date:	14-04-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-04-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-06-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-06-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-07-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	29-05-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	04-06-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2013-000281-11-NL
CCMO	NL43832.058.13
Other	volgt