A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VEMURAFENIB VERSUS VEMURAFENIB PLUS GDC-0973 IN PREVIOUSLY UNTREATED BRAFV600-MUTATION POSITIVE PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC MELANOMA

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

Summary

ID

NL-OMON44115

Source
ToetsingOnline

Brief title
coBrim GO28141

Condition

- Skin neoplasms malignant and unspecified

Synonym
Skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: F. Hoffman-La Roche ltd

Intervention

Keyword: cobimetinib (GDC-0973), Melanoma, Phase 3, Vemurafenib (Zelboraf)

Outcome measures

Primary outcome

The primary outcome measure for this study is as follows:

* PFS, defined as the time from randomization to the first occurrence of

disease progression, as determined by the investigator using RECIST v1.1, or

death from any cause, whichever comes first.

Secondary outcome

The secondary outcome measures are as follows:

* Overall survival, defined as the time from randomization to death from any

cause

* Objective response rate for patients with measurable disease at baseline,

defined as complete or partial response as assessed by investigator according

to RECIST v1.1

* Duration of response for patients with measurable disease at baseline,

defined as the time from first occurrence of a documented objective response

until the time of disease progression, as determined by investigator review of

tumor assessments using RECIST v1.1, or death from any cause during the study

(i.e., within 30 days after the last dose of study treatment)

* progression-free survival (PFS)

Study description

Background summary

Metastatic melanoma is one of the most deadly cancers, with a 5-year survival rate of 15% and a median overall survival of around 8 months.
The only medicinal products widely approved for the treatment of unresectable or metastatic melanoma are dacarbazine and ipilimumab, both of which require IV administration.
Vemurafenib is a compound (in tablet form) that selectively inhibits oncogenic BRAF kinase. Oncogenic mutations in BRAF kinase, predominantly V600E, have been observed in approximately 8% of all solid tumors, including 50% of metastatic melanomas. Discovery of oncogenic BRAF mutations highlights the central role of this kinase in signaling pathways that control cellular proliferation. The best-characterized substrate of BRAF is MEK kinase.
Oncogenic mutations in BRAF result in constitutive activation of BRAF kinase, which causes dysregulated downstream signaling via MEK and ERK, leading to excessive cell proliferation and survival.
The objective for the clinical investigation of the combination of vemurafenib with GDC-0973 (MEK inhibitor, in tablet form) is to simultaneously inhibit both oncogenic BRAF kinase (vemurafenib) and MEK (GDC-0973) in patients with previously untreated, BRAFV600E mutation-positive, locally advanced and unresectable or metastatic Melanoma.

The addition of a MEK inhibitor to vemurafenib abrogates vemurafenib resistance. These findings, together with preclinical evidence that combined inhibition of BRAF and MEK prevents the emergence of resistance support the clinical evaluation of combination therapy strategies incorporating MEK inhibition with BRAF inhibitors (BRAFi) in order to combat emerging resistance.

Study objective

Efficacy Objectives
The primary efficacy objective of study GO28141 is as follows:
* To evaluate the efficacy of vemurafenib in combination with GDC-0973, compared with vemurafenib and placebo, in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma, as measured by prolongation of progression-free survival (PFS), as assessed by the study site investigator.
The secondary efficacy objectives of study GO28141 are as follows:
* To evaluate the efficacy of vemurafenib in combination with GDC-0973, compared with vemurafenib and placebo, in previously untreated BRAFV600

mutation-positive patients with unresectable locally advanced or metastatic melanoma, as measured by overall survival (OS), objective response rate (ORR), and duration of response (DOR).
Safety Objectives
The safety objective of study GO28141 is as follows:
* To characterize the toxicity profile in patients receiving vemurafenib and GDC-0973 versus vemurafenib and placebo.
Pharmacokinetic Objectives
The pharmacokinetic (PK) objective of study GO28141 is as follows:
* To characterize the pharmacokinetics of GDC-0973 and vemurafenib and to compare the pharmacokinetics of vemurafenib when administered with GDC-0973 to the pharmacokinetics of vemurafenib when administered with placebo.
* To perform exploratory exposure-response analysis, including concentration-QT interval corrected (QTc) analysis.
Patient-Reported Outcome Objectives
The patient-reported outcome (PRO) objective of study GO28141 is as follows:
* To evaluate health-related quality of life in patients receiving vemurafenib and GDC-0973 versus vemurafenib and placebo as measured by the European Organization for Research and Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the EuroQol 5 dimension (EQ-5D) questionnaire.

Exploratory Objectives
The Sponsor is committed to the collection of biomarker samples in all clinical study protocols. The objective of biomarker profiling is to enable development of treatments specifically targeted for optimal patient benefit (personalized healthcare). Specimens may be used for any of the following:
* To explore the intrinsic and acquired mechanisms of resistance to MEK and BRAF inhibition in tumor samples obtained at baseline, during treatment, and at disease progression.
* To study the association of biomarkers with efficacy and/or adverse events (AEs) associated with medicinal products
* To increase knowledge and understanding of disease biology

Study design

GO28141 is a multicenter, randomized, double-blind, placebo-controlled Phase III clinical study to evaluate the safety and efficacy of vemurafenib in combination with GDC-0973 with vemurafenib alone.

Intervention

* Arm A (control arm): vemurafenib 960 mg by mouth (PO) twice daily (BID) on Days 1 * 28 and placebo PO once daily (QD) on Days 1 * 21 of each 28-day treatment cycle
* Arm B (investigational arm): vemurafenib 960 mg PO BID on Days 1 * 28 and GDC 0973 60 mg PO QD on Days 1 * 21 of each 28-day treatment cycle

Study burden and risks

Taking into account the efficacy and safety data of single-agent vemurafenib and GDC-0973 observed to date, and the favorable adverse effect profile of the combination observed in the Phase Ib study, the potential benefits of combination therapy and the extent of safety monitoring proposed, the potential benefit for patients with unresectable locally advanced or metastatic melanoma who participate in study GO28141 outweigh the potential risks.

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. Patients with histologically confirmed melanoma, either unresectable stage IIIc or stage IV

metastatic melanoma, as defined by the American Joint Committee on Cancer 7th edition. Unresectability of stage IIIc disease must have confirmation from a surgical oncologist.
2. Patients must be naïve to treatment for locally advanced unresectable or metastatic disease (i.e., NO prior systemic anti-cancer therapy for advanced disease; stage IIIc and IV). Prior adjuvant immunotherapy (including ipilimumab) is allowed.
3. Documentation of BRAFV600 mutation-positive status in melanoma tumor tissue (archival or newly obtained tumor samples) using the cobas 4800 BRAF V600 mutation test.
4. Male or female patient aged * 18 years.
5. Life expectancy * 12 weeks.

Exclusion criteria

1. History of prior RAF or MEK pathway inhibitor treatment.
2. Palliative radiotherapy within 14 days prior to the first dose of study treatment.
3. Major surgery or traumatic injury within 14 days prior to first dose of study treatment.
4. Active malignancy other than melanoma that could potentially interfere with the interpretation of efficacy measures. Patients with a previous malignancy within the past 3 years are excluded except for patients with resected basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) of the skin, melanoma in-situ, carcinoma in-situ of the cervix, and carcinoma in-situ of the breast.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-09-2013
Enrollment:	35

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	cobimetinib (GDC-0973)
Generic name:	cobimetinib (GDC-0973)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zelboraf
Generic name:	VEMURAFENIB
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-12-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-06-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-10-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-10-2013

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-12-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-04-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	02-04-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-10-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-03-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-03-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2012-003008-11-NL
ClinicalTrials.gov	NCT01689519
CCMO	NL42321.068.12