A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VEMURAFENIB (RO5185426) ADJUVANT THERAPY IN PATIENTS WITH SURGICALLY RESECTED, CUTANEOUS BRAF-MUTANT MELANOMA AT HIGH RISK FOR RECURRENCE

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Primary ObjectiveThe primary objective of this study is as follows:* To evaluate the efficacy of vemurafenib adjuvant treatment administered over a 52-week period in patients with completely resected BRAFV600 mutation*positive, cutaneous melanoma,...

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

Summary

ID

NL-OMON47343

Source
ToetsingOnline

Brief title
Roche GO27826 (BRIM8)

Condition

- Skin neoplasms malignant and unspecified
- Skin and subcutaneous tissue disorders NEC

Synonym

skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: Farmaceutical Industry

Intervention

Keyword: Melanoma, nodal metastasis, Vemurafenib

Outcome measures

Primary outcome

Efficacy Outcome Measures

* Disease-free survival (DFS) will be defined as the time from randomization

until the date of

the first local, regional, or distant melanoma recurrence ; occurrence of new

primary

melanoma; or death from any cause.

The DFS component of melanoma recurrence will be assessed by the investigator.

The DFS component of an occurrence of a new primary melanoma will be based upon

the diagnosis made by a Roche-designated central pathology laboratory.

Secondary outcome

* OS will be defined as the time from randomization to the date of death from

any cause.

* DMFS will be defined as the time from randomization until the date of

diagnosis of distant

(i.e., non-locoregional) metastases or death from any cause.

Study description

Background summary

Melanoma is one of the most deadly skin cancers. Detection and surgical treatment of early-stage disease seem to prevent progression in most cases. However, patients with deep primary tumors or tumors that metastasize to regional lymph nodes frequently develop distant metastases. The primary treatment modality for localized cutaneous melanoma is surgery. The only widely approved adjuvant therapy for melanoma patients at high risk for recurrence is interferon-alpha-2b with a high-dose regimen (PDR Network 2010). However, there is currently no international consensus regarding the dose, duration, or use of interferon-alpha-2b for the treatment of melanoma in the adjuvant setting (Hauschild et al. 2008). There is no generally accepted standard of care for adjuvant therapy in patients with resected cutaneous melanoma at high risk for recurrence that is both effective and well tolerated (Balch et al. 2009; Dummer et al. 2010). Recent advances in the understanding of the biology of melanoma have identified the role of BRAF kinase, a serine-threonine kinase downstream of RAS within the mitogenactivated protein kinase (MAPK) pathway. BRAF mutations have been identified in 50%*68% of metastatic melanomas, specifically melanomas that arise from intermittent sun-exposed skin (e.g., in superficial spreading and nodular melanomas) (Maldonado et al. 2003; Beeram et al. 2005; Curtin et al. 2005; Lang and MacKie 2005). Vemurafenib (formerly, RO5185426) is a low molecular weight, orally available inhibitor of the oncogenic form of the BRAF kinase commonly found in melanoma. It is a potent and highly selective inhibitor of V600-mutant BRAF. The clinical pharmacokinetics and safety of vemurafenib are based on data available from five studies in patients who received the commercial (microprecipitated bulk powder) formulation: NP22676, a cytochrome P450 (CYP) metabolism study in patients with BRAFV600 mutation-positive Stage IV melanoma (Genentech, data on file); NP25158, a mass balance study in patients with BRAFV600 mutation-positive Stage IV melanoma (Genentech, data on file); NP25163, a dose-escalation study in patients with BRAFV600 mutation*positive unresectable Stage IIIC or Stage IV melanoma (Genentech, data on file); NP22657, a Phase II, open-label study in patients with BRAFV600 mutation*positive Stage IV melanoma, in which the effects of vemurafenib on the QT interval were evaluated (Genentech, data on file); and NO25026, a Phase III, randomized, controlled study in patients with BRAFV600 mutation*positive unresectable Stage IIIC or Stage IV melanoma (Genentech, data on file). Efficacy was assessed in the following studies: PLX06-02, NP22657, NO25026. More detailed information on the findings of these studies can be found in the Vemurafenib Investigator*s Brochure. This Study (GO27826) is designed to evaluate the efficacy of vemurafenib adjuvant treatment administered over a 52-week period in patients with completely resected BRAFV600 mutation*positive, cutaneous melanoma, as measured by disease-free survival (DFS).

Please see section 1 (Background) of the protocol for additional study background information and section 10 (References) for cited references.

Study objective

Primary Objective
The primary objective of this study is as follows:
* To evaluate the efficacy of vemurafenib adjuvant treatment administered over a 52-week period in patients with completely resected BRAFV600 mutation* positive, cutaneous melanoma, as measured by disease-free survival (DFS)
Secondary Objectives
The secondary objectives of this study are as follows:
* To evaluate the efficacy of vemurafenib adjuvant treatment administered over a 52-week period, as measured by overall survival (OS)
* To evaluate the efficacy of vemurafenib adjuvant treatment administered over a 52-week period, as measured by distant metastasis-free survival (DMFS)
* To evaluate the safety and tolerability of vemurafenib in the adjuvant setting
* To assess quality of life as measured by European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30
* To describe the pharmacokinetics of vemurafenib in the adjuvant setting, assess between-patient variability of pharmacokinetic (PK) parameters, and explore and quantify potential covariates that may contribute to between-patient differences in PK parameters, using a population PK approach
Exploratory Objectives
The exploratory objectives of this study are as follows:
* To assess the efficacy outcomes and safety profile of vemurafenib adjuvant treatment in patients whose melanomas harbor non*E mutations of BRAF kinase at amino acid position 600, as detected by DNA sequencing methods
* To assess the relationship between vemurafenib exposure and the risk of melanoma recurrence, the occurrence of serious adverse events, and abnormalities in safety laboratory parameters
* To assess the relationship between biomarkers and risk of melanoma recurrence
* To characterize the biomarkers

Study design

Study GO27826 is a Phase III, international, multicenter, double-blind, randomized, placebo-controlled study of patients with completely resected, BRAFV600 mutation*positive melanoma, as detected by the cobas® BRAF V600 Mutation Test, at high risk for recurrence.
* Cohort 1 (approximately 300 patients) will include patients with completely resected Stage IIC, IIIA (patients with one or more nodal metastasis > 1 mm in diameter), or IIIB cutaneous melanoma as defined by the American Joint Committee on Cancer (AJCC)
Classification, v. 7 (Balch et al. 2009).
* Cohort 2 (approximately 225 patients) will include patients with Stage IIIC

cutaneous melanoma as defined by this classification scheme.
The primary and secondary efficacy and safety objectives of this study will be evaluated separately for each cohort.
Eligible patients will be randomized (1:1) to receive placebo or vemurafenib over a 52-week period, with randomization stratified by pathologic stage (Stage IIC, Stage IIIA, Stage IIIB) and region (North America; Australia/New Zealand/South Africa/Latin America; rest of the world)
in Cohort 1 and by region (North America; Australia/New Zealand/South Africa/Latin America; rest of the world) in Cohort 2.
Within each cohort, patients will receive study treatment according to one of the following treatment arms:
* Arm A: placebo orally, twice daily (BID) for 52 weeks (thirteen, 28-day cycles)
* Arm B: vemurafenib 960 mg orally, BID for 52 weeks (thirteen, 28-day cycles)

Intervention

* Cohort 1 (approximately 300 patients) will include patients with completely resected Stage IIC, IIIA (patients with one or more nodal metastasis > 1 mm in diameter), or IIIB cutaneous melanoma as defined by the American Joint Committee on Cancer (AJCC)
Classification, v. 7 (Balch et al. 2009).
* Cohort 2 (approximately 225 patients) will include patients with Stage IIIC cutaneous melanoma as defined by this classification scheme.

Eligible patients will be randomized (1:1) to receive placebo or vemurafenib over a 52-week period, with randomization stratified by pathologic stage (Stage IIC, Stage IIIA, Stage IIIB) and region (North America; Australia/New Zealand/South Africa/Latin America; rest of the world)
in Cohort 1 and by region (North America; Australia/New Zealand/South Africa/Latin America; rest of the world) in Cohort 2.
Within each cohort, patients will receive study treatment according to one of the following treatment arms:
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* Arm B: vemurafenib 960 mg orally, BID for 52 weeks (thirteen, 28-day cycles)

Study burden and risks

There is no consensus on standard care for adjuvant therapy for this patiengroup. And previous research with vemurafenib resulted in progression free survival. Because Vemurafenib demonstrated to be benificial in metastatic melanoma it might also be identified in patients with resected cutaneous melanoma who are at high risk for recurrence.

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

* Patients with completely resected, histologically confirmed, Stage IIC or Stage III, cutaneous melanoma where the BRAFV600 mutation status of the current primary tumor or involved lymph node is determined to be positive using the cobas® BRAF V600 Mutation Test. Patients with Stage IIIA disease must have at least one lymph node metastasis measuring > 1 mm in diameter
* Patients must have been surgically rendered free of disease within 70 days of randomization
* Eastern Cooperative Oncology Group performance status of 0 or 1
* Life expectancy of at least 5 years
* Patients must have fully recovered from the effects of any major surgery or significant traumatic injury prior to the first dose of study treatment

* Adequate hematologic, hepatic and renal function

Exclusion criteria

*History of any systemic or local therapy for the treatment of melanoma
*History of limb perfusion therapy
*History of radiotherapy for the treatment of melanoma
*Invasive malignancy other than melanoma at the time of enrollment or within 5 years prior to first dose of study treatment
*Known personal history of more than three (>3) adenomatous colorectal polyps or a personal history of adenomatous colorectal polyp(s) > 2 cm in size.This also applies to the screening colonoscopyfor select patients.
*Family history of colon cancer syndromes
*History of clinically significant cardiac or pulmonary dysfunction
*Major surgical procedure within 4 weeks prior to first dose of study treatment
*Infection with human immunodeficiency virus, hepatitis B or hepatitis C virus

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-09-2014
Enrollment:	14
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	17-10-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	18-04-2013
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	13-11-2013
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-12-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	07-05-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	17-07-2014
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	19-01-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	12-03-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-06-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-07-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-04-2016
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-05-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	11-07-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-01-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	30-04-2018
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2011-004011-24-NL
ClinicalTrials.gov	NCT01667419
CCMO	NL41606.058.12