Clinical trial results:
A Single-Arm, Open-Label, Expanded Access Study of Vemurafenib in Patients With Metastatic Melanoma

Summary

EudraCT number	2015-004211-20
Trial protocol	Outside EU/EEA
Global end of trial date	24 October 2011

Results information

Result version number	v1 (current)
This version publication date	26 January 2017
First version publication date	26 January 2017

Trial information

Trial identification

Sponsor protocol code	ML25597

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01248936
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 October 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 October 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To provide vemurafenib to patients with metastatic melanoma who are otherwise without satisfactory treatment options

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. A Data Review committee (DRC) supervised the participants' safety and performed the pre-specified interim analyses according to the protocol. Before entering the study, the informed consent form was read by and explained to all participants and/or their legally authorized representative. participants signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 December 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 371
Worldwide total number of subjects	371
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	1

Adults (18-64 years)	289
From 65 to 84 years	79
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 29 study sites in the United States (US). In all 374 participants were enrolled in the study and 371 received the study medication.

Pre-assignment

Screening details:

Overall, 745 participants were screened during the study, of which 371 were randomized to receive study treatment; the main reason for screen failure was negative cobas test, consent withdrawal, BRAF test not performed, patient died or progressed.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall trial

Arm description:

Participants received vemurafenib 960 milligram (mg) orally two times a day for up to one year. Participants were treated until disease progression, unmanageable toxicity most probably attributable to vemurafenib, withdrawal of consent, and study termination by the sponsor.

Arm type	Experimental
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	RO5185426
Other name	PLX4032, or RG7204
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vemurafenib was administered 960 mg (four tablets of 240 mg each) orally two times a day for up to one year

Number of subjects in period 1	Overall trial
Started	371
Completed	0
Not completed	371
Adverse event, not serious	2
Consent withdrawn by subject	20
Progression of Disease	50
Death	26
Refused Treatment	1
Adverse event, serious non-fatal	6
Lost to follow-up	7
Sponsor Decision (Switch to Commercial Drug)	259

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description:

Participants received vemurafenib 960 milligram (mg) orally two times a day for up to one year. Participants were treated until disease progression, unmanageable toxicity most probably attributable to vemurafenib, withdrawal of consent, and study termination by the sponsor.

Reporting group values	Overall trial	Total	
Number of subjects	371	371	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	289	289	
From 65-84 years	79	79	
85 years and over	2	2	
Age continuous Units: years			
arithmetic mean	53.5		
standard deviation	± 13.8	-	
Gender categorical Units: Subjects			
Female	142	142	
Male	229	229	

End points

End points reporting groups

Reporting group title	Overall trial

Reporting group description:

Participants received vemurafenib 960 milligram (mg) orally two times a day for up to one year. Participants were treated until disease progression, unmanageable toxicity most probably attributable to vemurafenib, withdrawal of consent, and study termination by the sponsor.

Primary: Number of Participants With Any Adverse Event, Adverse Events With Severity, Adverse Events Leading to Discontinuation

End point title	Number of Participants With Any Adverse Event, Adverse Events With Severity, Adverse Events Leading to Discontinuation[1]

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs will be graded according to the 'National Cancer Institute Common Terminology Criteria for Adverse Events' (NCI CTCAE, v4.0). However Laboratory data will be summarized by grade using the NCI CTCAE, v4.0 toxicity grade.

End point type	Primary

End point timeframe:

Up to 1 year

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Study data were analyzed by descriptive summaries. No formal hypothesis testing was planned.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	371			
Units: Number of Participants				
Any AE	346			
Grade 3 AEs	115			
Grade 4 AEs	15			
Grade 5 AEs	7			
AEs leading to discontinuation	9			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Any Serious Adverse Event, Death and Cause of Death

End point title	Number of Participants With Any Serious Adverse Event, Death and Cause of Death[2]

End point description:

Serious Adverse Event (SAEs) is defined as those events that were fatal or immediately life-threatening, and those events that resulted in hospitalization; prolonged an existing hospitalization; resulted in

disability; or was a congenital anomaly. Number of participants who died and the cause of death are also recorded.

End point type	Primary

End point timeframe:

Up to 1 year

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Study data were analyzed by descriptive summaries. No formal hypothesis testing was planned.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	371			
Units: Number of Participants				
Any SAEs	83			
All Deaths	43			
Death due to progression of disease	22			
Death due to adverse event	8			
Deaths which are not related to study drug	6			
Deaths which are related to study drug	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Best Overall Response (Unconfirmed)

End point title	Number of Participants With Best Overall Response (Unconfirmed)

End point description:

The best overall response (unconfirmed) is the best response recorded from the start of the treatment until disease progression/recurrence which was unconfirmed. Participants were assessed for best overall response by investigator as per 'Response Evaluation Criteria in Solid Tumors' (RECIST v1.1).

End point type	Secondary

End point timeframe:

Up to 1 year

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	241			
Units: Number of Participants				
Unconfirmed objective response	129			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Best Overall Response (Unconfirmed) by ECOG Performance

End point title	Number of Participants With Best Overall Response (Unconfirmed) by ECOG Performance

End point description:

The best overall response recorded from the start of the treatment until disease progression/recurrence which was unconfirmed in patients with Eastern Cooperative Oncology Group (ECOG) performance status 2 or 3/0 or 1. This endpoint was tumor response category according to investigator assessment per RECIST v1.1 for efficacy assessment. The 'n' is number of participants with ECOG performance status in each criteria.

End point type	Secondary

End point timeframe:

Up to 1 year

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	241			
Units: Number of Participants				
ECOG performance status 2 or 3, n=31	13			
ECOG performance status 0 or 1, n=210	116			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Best Overall Response (Confirmed)

End point title	Number of Participants With Best Overall Response (Confirmed)

End point description:

The best overall response (confirmed) is the best response recorded from the start of the treatment until disease progression/recurrence which was confirmed. Participants were assessed for best overall response by investigator as per RECIST v1.1.

End point type	Secondary

End point timeframe:

Up to 1 year

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	241			
Units: Number of Participants				
Confirmed objective response	26			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Best Overall Response (Confirmed) by ECOG Performance

End point title	Number of Participants With Best Overall Response (Confirmed) by ECOG Performance

End point description:

] The best overall response recorded from the start of the treatment until disease progression/recurrence which was confirmed in patients with Eastern Cooperative Oncology Group (ECOG) performance status 2 or 3/0 or 1. Participants were assessed for best overall response by investigator as per RECIST v1.1. The 'n' is number of participants with ECOG performance status in each criteria.

End point type	Secondary

End point timeframe:

Up to 1 year

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	241			
Units: Number of Participants				
ECOG performance status 2 or 3; n=31	1			
ECOG performance status 0 or 1; n=210	25			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Time to Complete Response/Partial Response

End point title	Mean Time to Complete Response/Partial Response

End point description:

Mean time to Complete Response (CR)/Partial Response(PR) (confirmed or unconfirmed was assessed). Participants were assessed for best overall response by investigator as per RECIST v1.1.

End point type	Secondary

End point timeframe:

Up to 1 year

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	241			
Units: Months				
arithmetic mean (standard deviation)				
Mean time to confirmed CR or PR	1.8 (± 0.3)			
Mean time to unconfirmed CR or PR	2 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 1 Year

Adverse event reporting additional description:

Serious adverse events and non-serious adverse events are reported in safety analysis set, which consists of all participants who received at least one dose of study medication and had a safety assessment performed post baseline.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Participants received vemurafenib 960 milligram (mg) orally two times a day for up to one year. Participants were treated until disease progression, unmanageable toxicity most probably attributable to vemurafenib, withdrawal of consent, and study termination by the sponsor.

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	83 / 371 (22.37%)		
number of deaths (all causes)	43		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	5 / 371 (1.35%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	2 / 371 (0.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Asthenia				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drug withdrawal syndrome				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Pain				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Female genital tract fistula				

subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 371 (0.81%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	3 / 371 (0.81%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 1		
Pulmonary embolism			
subjects affected / exposed	2 / 371 (0.54%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary haemorrhage			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	3 / 371 (0.81%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	2 / 371 (0.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Paranoia			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 371 (0.81%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood uric acid increased			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			

subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	5 / 371 (1.35%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	2 / 371 (0.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Hydrocephalus			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Lethargy			

subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar radiculopathy			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Paraesthesia			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Spinal cord compression			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 371 (0.81%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Lymphopenia			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Pupils unequal			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Uveitis			

subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 371 (1.35%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	3 / 371 (0.81%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	2 / 371 (0.54%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticular perforation			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dermatitis			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Photosensitivity reaction			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Renal colic				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	2 / 371 (0.54%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	2 / 371 (0.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	4 / 371 (1.08%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			

Urinary tract infection				
subjects affected / exposed	4 / 371 (1.08%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	3 / 371 (0.81%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Bacterial infection				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridial infection				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	5 / 371 (1.35%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	2 / 371 (0.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed	1 / 371 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				

subjects affected / exposed	1 / 371 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	308 / 371 (83.02%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	25 / 371 (6.74%)		
occurrences (all)	48		
Skin papilloma			
subjects affected / exposed	23 / 371 (6.20%)		
occurrences (all)	27		
Investigations			
Weight decreased			
subjects affected / exposed	27 / 371 (7.28%)		
occurrences (all)	28		
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	48 / 371 (12.94%)		
occurrences (all)	51		
Nervous system disorders			
Headache			
subjects affected / exposed	37 / 371 (9.97%)		
occurrences (all)	39		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	102 / 371 (27.49%)		
occurrences (all)	108		
Oedema peripheral			
subjects affected / exposed	41 / 371 (11.05%)		
occurrences (all)	46		
Pyrexia			

subjects affected / exposed	37 / 371 (9.97%)		
occurrences (all)	43		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	69 / 371 (18.60%)		
occurrences (all)	75		
Diarrhoea			
subjects affected / exposed	42 / 371 (11.32%)		
occurrences (all)	43		
Vomiting			
subjects affected / exposed	30 / 371 (8.09%)		
occurrences (all)	32		
Constipation			
subjects affected / exposed	20 / 371 (5.39%)		
occurrences (all)	20		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	102 / 371 (27.49%)		
occurrences (all)	115		
Photosensitivity reaction			
subjects affected / exposed	62 / 371 (16.71%)		
occurrences (all)	65		
Alopecia			
subjects affected / exposed	41 / 371 (11.05%)		
occurrences (all)	41		
Hyperkeratosis			
subjects affected / exposed	29 / 371 (7.82%)		
occurrences (all)	29		
Dry skin			
subjects affected / exposed	26 / 371 (7.01%)		
occurrences (all)	26		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	23 / 371 (6.20%)		
occurrences (all)	24		
Pruritus			

subjects affected / exposed	36 / 371 (9.70%)		
occurrences (all)	40		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	136 / 371 (36.66%)		
occurrences (all)	147		
Myalgia			
subjects affected / exposed	30 / 371 (8.09%)		
occurrences (all)	33		
Pain in extremity			
subjects affected / exposed	20 / 371 (5.39%)		
occurrences (all)	26		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	42 / 371 (11.32%)		
occurrences (all)	45		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2010	In this protocol amendment, the eligible patient population was limited to patients who had received prior systemic therapy for metastatic melanoma, since broader evidence for efficacy and safety of vemurafenib in patients with metastatic melanoma. In addition to head and neck, dermatological, and chest CT examinations, further assessments (examination of anus and for woman in addition pelvic examination)were introduced at baseline and at the end of study to more closely monitor the risk for SCC.
07 February 2011	In this protocol amendment, new information has been added to Sections 3.4 (Safety Plan) and 4.3.2 (Dosage and Administration) that describes how dosing of vemurafenib should be modified according to QTc interval. Related to this, in Section 4.5.3 (Assessments during treatment) and Appendix A of the protocol (Study Flowchart), 12-lead ECGs became mandatory and occurred >= 4 weeks after study drug initiation, monthly for the next 3 months, and every 3 months thereafter. The earliest age at which patients were eligible was reduced from 18 years to 16 years.
05 May 2011	In this protocol amendment, the patients with melanoma brain metastases, with unresectable Stage IIIc metastatic melanoma, and with concurrent malignancies for which therapeutic intervention was not warranted became eligible. Performance status for eligibility was broadened from a performance status of 0–2 to a performance status of 0–3. The dosage of vemurafenib was no longer allowed to be reduced to 480 mg b.i.d. if an increase in QTc > 500 msec or a change from baseline > 60 msec was observed after a prior dose reduction from 960 mg b.i.d. to 720 mg b.i.d. Patients with a history of long QT syndrome were explicitly excluded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported