Clinical trial results:
An Open-label, Single-arm, Phase II, Multicentre Study to Evaluate the Efficacy of Vemurafenib in Metastatic Melanoma Patients with Brain Metastases

Summary

EudraCT number	2011-000954-46
Trial protocol	DE ES GB IT
Global end of trial date	21 July 2015

Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	06 July 2016

Trial information

Trial identification

Sponsor protocol code	MO25743

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01378975
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	F.Hoffmann-La Roche AG., F.Hoffmann-La Roche AG., 41 616878333, global.trial_information@roche.com
Scientific contact	F.Hoffmann-La Roche AG., 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	21 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To evaluate the efficacy of vemurafenib using Best Overall Response Rate (BORR), as assessed by an Independent Review Committee (IRC) using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST, v1.1) in the brain of metastatic melanoma subjects with previously untreated brain metastases.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	146
EEA total number of subjects	102

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)	0
Adults (18-64 years)	108
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 289 subjects with metastatic melanoma were screened for entry into the study, out of which 146 subjects were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Previously Untreated Subjects

Arm description:

Subjects who had not received previous treatment for brain metastases [i.e., had never received brain stereotactic radiotherapy (SRT), whole-brain radiotherapy (WBRT), surgery, or any other treatment for their brain metastases] received Vemurafenib 960 milligram (mg) tablet orally, twice daily (BID) from Day 1 until development of progressive disease within the brain or outside of the brain (whichever occurred first), unacceptable toxicity, consent withdrawal, protocol violation endangering subject's safety, death, reasons deemed by the investigator, or study termination by the Sponsor.

Arm type	Experimental
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

960 milligram (mg) oral doses twice daily from day 1 until disease progression, unacceptable toxicity or consent withdrawal.

Arm title	Cohort 2: Previously Treated Subjects

Arm description:

Subjects who were previously treated with brain SRT, WBRT, or surgery for their brain metastases and have progressed following this treatment, received Vemurafenib 960 milligram (mg) tablet orally, BID from Day 1 until development of progressive disease within the brain or outside of the brain (whichever occurred first), unacceptable toxicity, consent withdrawal, protocol violation endangering subject's safety, death, reasons deemed by the investigator, or study termination by the Sponsor.

Arm type	Experimental
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

960 mg oral doses twice daily from Day 1 until disease progression, unacceptable toxicity or consent withdrawal.

Number of subjects in period 1	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects
Started	90	56
Completed	4	6
Not completed	86	50
Withdrew Consent	4	3
Investigator Request	1	-
Death	77	46
Lost to follow-up	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Previously Untreated Subjects
Reporting group description:	
Subjects who had not received previous treatment for brain metastases [i.e., had never received brain stereotactic radiotherapy (SRT), whole-brain radiotherapy (WBRT), surgery, or any other treatment for their brain metastases] received Vemurafenib 960 milligram (mg) tablet orally, twice daily (BID) from Day 1 until development of progressive disease within the brain or outside of the brain (whichever occurred first), unacceptable toxicity, consent withdrawal, protocol violation endangering subject's safety, death, reasons deemed by the investigator, or study termination by the Sponsor.	
Reporting group title	Cohort 2: Previously Treated Subjects
Reporting group description:	
Subjects who were previously treated with brain SRT, WBRT, or surgery for their brain metastases and have progressed following this treatment, received Vemurafenib 960 milligram (mg) tablet orally, BID from Day 1 until development of progressive disease within the brain or outside of the brain (whichever occurred first), unacceptable toxicity, consent withdrawal, protocol violation endangering subject's safety, death, reasons deemed by the investigator, or study termination by the Sponsor.	

Reporting group values	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects	Total
Number of subjects	90	56	146
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	55.7	52.7	
standard deviation	± 12.73	± 13.85	-
Gender categorical Units: Subjects			
Female	34	22	56
Male	56	34	90

End point values	Cohort 1: Previously Untreated Subjects			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: percentage of subjects				
number (confidence interval 95%)	17.8 (10.5 to 27.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (BORR) in the Brain of Subjects With Previously Treated or Untreated Brain Metastases as Assessed by the IRC Using RECIST v1.1

End point title	Best Overall Response Rate (BORR) in the Brain of Subjects With Previously Treated or Untreated Brain Metastases as Assessed by the IRC Using RECIST v1.1

End point description:

Percentage of subjects who were responders with best overall response (BOR) documented as confirmed CR, PR, SD, PD. CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The ITT population included all subjects who were enrolled in the study.

End point type	Secondary

End point timeframe:

From the date of randomisation until the disease progression or death from any cause (approximately 4 years)

End point values	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	56		
Units: percentage of subjects				
number (not applicable)				
Complete Response	2.2	0		
Partial Response	15.6	17.9		
Stable Disease	43.3	41.1		
Progressive Disease	32.2	33.9		
Unevaluable	6.7	7.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (BORR) in the Brain of Subject With Previously Treated Brain Metastases as Assessed by the IRC Using RECIST v1.1

End point title	Best Overall Response Rate (BORR) in the Brain of Subject With Previously Treated Brain Metastases as Assessed by the IRC Using RECIST v1.1[3]

End point description:

BORR within brain assessed by IRC is defined as percentage of subjects who were responders (with BOR documented as confirmed CR or PR). According to RECIST v1.1 criteria modified for brain metastases, CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm, PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The ITT population included all subjects who were enrolled in the study.

End point type	Secondary

End point timeframe:

From the date of randomisation until the disease progression or death from any cause (approximately 4 years)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data for this endpoint was planned to be reported for one reporting arm (Cohort 2: Previously Treated Subjects).

End point values	Cohort 2: Previously Treated Subjects			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: percentage of subjects				
number (confidence interval 95%)	17.9 (8.9 to 30.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate Outside the Brain (Assessed by IRC)

End point title	Best Overall Response Rate Outside the Brain (Assessed by IRC)

End point description:

BORR outside of brain assessed by IRC is defined as percentage of subjects who were responders (with BOR documented as confirmed CR or PR). According to RECIST v1.1 criteria modified for brain metastases, CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm, PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The ITT population included all subject who were enrolled in the study. Here, number of subjects analysed is the total number of subjects who had measurable disease outside brain at Baseline.

End point type	Secondary

End point timeframe:

From the date of randomisation until the disease progression or death from any cause (approximately 4 years)

End point values	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	49		
Units: percentage of subjects				
number (confidence interval 95%)	32.9 (22.7 to 44.4)	22.5 (10.8 to 38.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) (Assessed by Investigator and IRC)

End point title	Duration of Response (DOR) (Assessed by Investigator and IRC)

End point description:

Duration of response was defined as the time interval between the date of the earliest qualifying response and the earliest date of PD or death from any cause. For subject who were alive without progression following the qualifying response, DOR were censored on the date of last available tumor assessment on or before the data cutoff date. The ITT population included all subjects who were enrolled in the study. Here, 'n' indicates number of subjects who were responders within brain or outside brain assessed by investigator or IRC.

End point type	Secondary

End point timeframe:

Date of the earliest qualifying response until the earliest date of PD or death from any cause (approximately up to 4 years)

End point values	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	56		
Units: months				
median (full range (min-max))				
Investigator: DOR (Within Brain) (n=26, 13)	4.67 (2.66 to 24.21)	6.64 (1.87 to 21.98)		
Investigator: DOR (Outside Brain) (n=25, 11)	5.55 (1.84 to 25.63)	10.74 (1.84 to 23.1)		
IRC: DOR (Within Brain) (n=16, 10)	4.6 (2.66 to 29.9)	6.64 (0.95 to 18.4)		
IRC: DOR (Outside Brain) (n=26, 9)	7.72 (1.84 to 21.55)	11.07 (1.84 to 23.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Based on Overall Tumor Response (Assessed by Investigator)

End point title	Progression-Free Survival (PFS) Based on Overall Tumor Response (Assessed by Investigator)

End point description:

Progression-free survival was defined as the time between enrollment on Day 1 and the date of first radiographically documented progressive disease (within or outside the brain), clinical progressive disease, as assessed by the investigator or death whichever occurred first. The ITT population included all subjects who were enrolled in the study.

End point type	Secondary

End point timeframe:

From the date of randomisation until the disease progression or death from any cause (approximately 4 years)

End point values	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	56		
Units: months				
median (full range (min-max))	3.65 (0.3 to 33.35)	3.71 (0.26 to 27.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Based on Tumor Assessment Within Brain Only (Assessed by Investigator)

End point title	Progression-Free Survival (PFS) Based on Tumor Assessment Within Brain Only (Assessed by Investigator)

End point description:

Progression-free survival was defined as the time between enrollment on Day 1 and the date of first radiographically documented progressive disease (within brain), clinical progressive disease, as assessed by the investigator or death whichever occurred first. The ITT population included all subjects who were enrolled in the study.

End point type	Secondary

End point timeframe:

From the date of randomisation until the disease progression or death from any cause (approximately 4

years)

End point values	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	56		
Units: months				
median (full range (min-max))	3.68 (0.36 to 33.35)	4.04 (0.26 to 27.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Development of New Brain Metastases in Responders

End point title	Time to Development of New Brain Metastases in Responders

End point description:

Time to development of new lesions within the brain was defined as the interval between the date of first treatment and the earliest date of documentation of new brain lesions. Subjects who were known to be free of new lesions were censored on the date of last tumor assessment. The ITT population included all subjects who were enrolled in the study. Here, number of subjects analysed is the subjects who were responders.

End point type	Secondary

End point timeframe:

Date of first treatment and the earliest date of documentation of new brain lesions (approximately up to 4 years)

End point values	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	13		
Units: months				
median (full range (min-max))	14.92 (3.48 to 33.35)	14.52 (2.79 to 27.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as time between enrollment on Day 1 and date of death, irrespective of the cause of death. Subjects for whom no death was captured on the clinical database were censored at the latest date they were known to be alive prior to or on the cutoff date. The ITT population included all subject who were enrolled in the study.

End point type	Secondary

End point timeframe:

From the date of randomisation until the disease progression or death from any cause (approximately 4 years)

End point values	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	56		
Units: months				
median (full range (min-max))	8.87 (0.59 to 34.53)	9.63 (0.66 to 34.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (BORR) Within the Brain and Outside Brain (Assessed by Investigator)

End point title	Best Overall Response Rate (BORR) Within the Brain and Outside Brain (Assessed by Investigator)

End point description:

Percentage of subjects who were responders with BOR documented as confirmed CR or PR, SD, PD. CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: At least a 30% decrease in sum of diameters of target lesions, taking as reference baseline sum diameters. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference smallest sum diameters while on study. PD: at least a 20% increase in sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. ITT population. Here, 'n' indicates the number subjects who were evaluable for within brain assessment and who had measurable disease outside brain at baseline for outside brain assessment.

End point type	Secondary

End point timeframe:

From the date of randomisation until the disease progression or death from any cause (approximately 4 years)

End point values	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	56		
Units: percentage of subjects				
number (not applicable)				
Complete Response (Within Brain) (n=90, 56)	2.2	0		
Partial Response (Within Brain) (n=90, 56)	26.7	23.2		
Stable Disease (Within Brain) (n=90, 56)	40	53.6		
Progressive Disease (Within Brain) (n=90, 56)	27.8	19.6		
Unevaluable (Within Brain) (n=90, 56)	3.3	3.6		
Complete Response (Outside Brain) (n=79, 40)	0	5		
Partial Response (Outside Brain) (n=79, 40)	31.6	22.5		
Stable Disease (Outside Brain) (n=79, 40)	49.4	52.5		
Progressive Disease (Outside Brain) (n=79, 40)	11.4	15		
Unevaluable (Outside Brain) (n=79, 40)	7.6	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (BORR) Within the Brain and Outside Brain (Not Necessarily Follows the RECIST Criteria - as Assessed by Investigator)

End point title	Best Overall Response Rate (BORR) Within the Brain and Outside Brain (Not Necessarily Follows the RECIST Criteria - as Assessed by Investigator)

End point description:

Percentage of subject who were responders (with BOR documented as confirmed CR or PR) were reported. The ITT population included all subjects who were enrolled in the study.

End point type	Secondary

End point timeframe:

From the date of randomisation until the disease progression or death from any cause (approximately 4 years)

End point values	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	56		
Units: percentage of subjects				
number (confidence interval 95%)	18.9 (11.4 to	17.9 (8.9 to		

28.5)	30.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AE)

End point title	Percentage of Subjects With Adverse Events (AE)

End point description:

An AE was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. The safety population included all subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

From signing of informed consent form up to 28 days after the last dose of study drug (approximately up to 4 years)

End point values	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	56		
Units: percentage of subjects				
number (not applicable)	97.8	94.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent form up to 28 days after the last dose of study drug (Up to approximately 4 years)

Adverse event reporting additional description:

The safety population included all subject who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Cohort 1: Previously Untreated Subjects

Reporting group description:

Subjects who had not received previous treatment for brain metastases [i.e., had never received brain stereotactic radiotherapy (SRT), whole-brain radiotherapy (WBRT), surgery, or any other treatment for their brain metastases] received Vemurafenib 960 milligram (mg) tablet orally, twice daily (BID) from Day 1 until development of progressive disease within the brain or outside of the brain (whichever occurred first), unacceptable toxicity, consent withdrawal, protocol violation endangering subject's safety, death, reasons deemed by the investigator, or study termination by the Sponsor.

Reporting group title	Cohort 2: Previously Treated Subjects

Reporting group description:

Subjects who were previously treated with brain SRT, WBRT, or surgery for their brain metastases and have progressed following this treatment, received Vemurafenib 960 milligram (mg) tablet orally, BID from Day 1 until development of progressive disease within the brain or outside of the brain (whichever occurred first), unacceptable toxicity, consent withdrawal, protocol violation endangering subject's safety, death, reasons deemed by the investigator, or study termination by the Sponsor.

Serious adverse events	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 90 (41.11%)	27 / 56 (48.21%)	
number of deaths (all causes)	77	46	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	11 / 90 (12.22%)	6 / 56 (10.71%)	
occurrences causally related to treatment / all	19 / 19	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	11 / 90 (12.22%)	4 / 56 (7.14%)	
occurrences causally related to treatment / all	14 / 14	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malignant melanoma			
subjects affected / exposed	2 / 90 (2.22%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioma			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar neoplasm benign			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 90 (2.22%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 90 (0.00%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis constrictive			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 90 (1.11%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Seizure			
subjects affected / exposed	1 / 90 (1.11%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Iridocyclitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular ischaemic syndrome			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloedema			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 90 (2.22%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			

subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc degeneration			

subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 90 (1.11%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Abscess rupture			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural cellulitis			

subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1: Previously Untreated Subjects	Cohort 2: Previously Treated Subjects	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 90 (94.44%)	53 / 56 (94.64%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	7 / 90 (7.78%)	1 / 56 (1.79%)	
occurrences (all)	7	1	
Basal cell carcinoma			
subjects affected / exposed	1 / 90 (1.11%)	3 / 56 (5.36%)	
occurrences (all)	1	3	
Skin papilloma			

subjects affected / exposed	15 / 90 (16.67%)	12 / 56 (21.43%)	
occurrences (all)	17	13	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 90 (6.67%)	4 / 56 (7.14%)	
occurrences (all)	7	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	22 / 90 (24.44%)	19 / 56 (33.93%)	
occurrences (all)	26	25	
Asthenia			
subjects affected / exposed	13 / 90 (14.44%)	6 / 56 (10.71%)	
occurrences (all)	14	8	
Oedema peripheral			
subjects affected / exposed	7 / 90 (7.78%)	8 / 56 (14.29%)	
occurrences (all)	8	14	
Pyrexia			
subjects affected / exposed	11 / 90 (12.22%)	7 / 56 (12.50%)	
occurrences (all)	11	8	
Pain			
subjects affected / exposed	6 / 90 (6.67%)	5 / 56 (8.93%)	
occurrences (all)	6	5	
Chest pain			
subjects affected / exposed	1 / 90 (1.11%)	4 / 56 (7.14%)	
occurrences (all)	2	4	
Xerosis			
subjects affected / exposed	5 / 90 (5.56%)	1 / 56 (1.79%)	
occurrences (all)	5	1	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 90 (0.00%)	3 / 56 (5.36%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 90 (8.89%)	6 / 56 (10.71%)	
occurrences (all)	8	6	

Dyspnoea			
subjects affected / exposed	5 / 90 (5.56%)	3 / 56 (5.36%)	
occurrences (all)	7	3	
Oropharyngeal pain			
subjects affected / exposed	3 / 90 (3.33%)	3 / 56 (5.36%)	
occurrences (all)	3	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 90 (5.56%)	7 / 56 (12.50%)	
occurrences (all)	5	10	
Confusional state			
subjects affected / exposed	0 / 90 (0.00%)	4 / 56 (7.14%)	
occurrences (all)	0	4	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	22 / 90 (24.44%)	8 / 56 (14.29%)	
occurrences (all)	26	13	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 90 (6.67%)	3 / 56 (5.36%)	
occurrences (all)	10	4	
Blood bilirubin increased			
subjects affected / exposed	6 / 90 (6.67%)	4 / 56 (7.14%)	
occurrences (all)	10	4	
Alanine aminotransferase increased			
subjects affected / exposed	6 / 90 (6.67%)	5 / 56 (8.93%)	
occurrences (all)	8	5	
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 90 (5.56%)	2 / 56 (3.57%)	
occurrences (all)	11	2	
Weight decreased			
subjects affected / exposed	6 / 90 (6.67%)	6 / 56 (10.71%)	
occurrences (all)	6	6	
Blood creatinine increased			
subjects affected / exposed	5 / 90 (5.56%)	3 / 56 (5.36%)	
occurrences (all)	7	3	
Injury, poisoning and procedural complications			

Sunburn			
subjects affected / exposed	6 / 90 (6.67%)	2 / 56 (3.57%)	
occurrences (all)	6	3	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 90 (17.78%)	8 / 56 (14.29%)	
occurrences (all)	20	9	
Paraesthesia			
subjects affected / exposed	9 / 90 (10.00%)	2 / 56 (3.57%)	
occurrences (all)	9	2	
Dysgeusia			
subjects affected / exposed	6 / 90 (6.67%)	4 / 56 (7.14%)	
occurrences (all)	6	4	
Seizure			
subjects affected / exposed	2 / 90 (2.22%)	6 / 56 (10.71%)	
occurrences (all)	2	6	
Dizziness			
subjects affected / exposed	3 / 90 (3.33%)	3 / 56 (5.36%)	
occurrences (all)	3	3	
Balance disorder			
subjects affected / exposed	0 / 90 (0.00%)	3 / 56 (5.36%)	
occurrences (all)	0	5	
Tremor			
subjects affected / exposed	0 / 90 (0.00%)	5 / 56 (8.93%)	
occurrences (all)	0	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 90 (7.78%)	6 / 56 (10.71%)	
occurrences (all)	8	7	
Neutropenia			
subjects affected / exposed	1 / 90 (1.11%)	3 / 56 (5.36%)	
occurrences (all)	1	3	
Eye disorders			
Photophobia			
subjects affected / exposed	2 / 90 (2.22%)	3 / 56 (5.36%)	
occurrences (all)	2	3	
Visual impairment			

subjects affected / exposed	1 / 90 (1.11%)	3 / 56 (5.36%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	15 / 90 (16.67%)	14 / 56 (25.00%)	
occurrences (all)	19	17	
Diarrhoea			
subjects affected / exposed	14 / 90 (15.56%)	10 / 56 (17.86%)	
occurrences (all)	16	13	
Vomiting			
subjects affected / exposed	8 / 90 (8.89%)	8 / 56 (14.29%)	
occurrences (all)	9	13	
Constipation			
subjects affected / exposed	5 / 90 (5.56%)	2 / 56 (3.57%)	
occurrences (all)	6	2	
Abdominal pain upper			
subjects affected / exposed	1 / 90 (1.11%)	3 / 56 (5.36%)	
occurrences (all)	1	3	
Dyspepsia			
subjects affected / exposed	0 / 90 (0.00%)	3 / 56 (5.36%)	
occurrences (all)	0	3	
Faecal incontinence			
subjects affected / exposed	0 / 90 (0.00%)	3 / 56 (5.36%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Hyperkeratosis			
subjects affected / exposed	28 / 90 (31.11%)	13 / 56 (23.21%)	
occurrences (all)	39	16	
Rash			
subjects affected / exposed	29 / 90 (32.22%)	17 / 56 (30.36%)	
occurrences (all)	36	19	
Photosensitivity reaction			
subjects affected / exposed	18 / 90 (20.00%)	17 / 56 (30.36%)	
occurrences (all)	22	19	
Erythema			

subjects affected / exposed	13 / 90 (14.44%)	9 / 56 (16.07%)	
occurrences (all)	20	13	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	7 / 90 (7.78%)	8 / 56 (14.29%)	
occurrences (all)	19	12	
Alopecia			
subjects affected / exposed	16 / 90 (17.78%)	13 / 56 (23.21%)	
occurrences (all)	16	13	
Pruritus			
subjects affected / exposed	16 / 90 (17.78%)	6 / 56 (10.71%)	
occurrences (all)	20	6	
Dry skin			
subjects affected / exposed	11 / 90 (12.22%)	10 / 56 (17.86%)	
occurrences (all)	12	10	
Actinic keratosis			
subjects affected / exposed	6 / 90 (6.67%)	5 / 56 (8.93%)	
occurrences (all)	8	5	
Keratosis pilaris			
subjects affected / exposed	9 / 90 (10.00%)	2 / 56 (3.57%)	
occurrences (all)	9	2	
Dermal cyst			
subjects affected / exposed	4 / 90 (4.44%)	3 / 56 (5.36%)	
occurrences (all)	5	3	
Rash follicular			
subjects affected / exposed	1 / 90 (1.11%)	3 / 56 (5.36%)	
occurrences (all)	1	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	31 / 90 (34.44%)	23 / 56 (41.07%)	
occurrences (all)	44	30	
Pain in extremity			
subjects affected / exposed	8 / 90 (8.89%)	5 / 56 (8.93%)	
occurrences (all)	9	6	
Myalgia			

subjects affected / exposed	8 / 90 (8.89%)	5 / 56 (8.93%)	
occurrences (all)	9	5	
Musculoskeletal pain			
subjects affected / exposed	6 / 90 (6.67%)	3 / 56 (5.36%)	
occurrences (all)	6	6	
Back pain			
subjects affected / exposed	5 / 90 (5.56%)	1 / 56 (1.79%)	
occurrences (all)	5	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 90 (5.56%)	4 / 56 (7.14%)	
occurrences (all)	5	5	
Upper respiratory tract infection			
subjects affected / exposed	2 / 90 (2.22%)	4 / 56 (7.14%)	
occurrences (all)	2	4	
Urinary tract infection			
subjects affected / exposed	2 / 90 (2.22%)	4 / 56 (7.14%)	
occurrences (all)	2	4	
Conjunctivitis			
subjects affected / exposed	2 / 90 (2.22%)	3 / 56 (5.36%)	
occurrences (all)	2	3	
Folliculitis			
subjects affected / exposed	0 / 90 (0.00%)	3 / 56 (5.36%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2012	• The start-of-screening date was taken as date on which first archival tumor tissue sample was sent (collected by courier) to the central testing laboratory for BRAF mutation testing EXCEPT when a study procedure is performed prior to sending tumor sample to laboratory (e.g., if a new tumor biopsy sample must be taken from subject). • Monitoring of any possible additional cancerous growths and determination of their type(s) was added to the study procedures during the screening period, treatment period, treatment discontinuation, and follow-up visit. The ICF also was updated with this information. • A clarification was added denoting that only a protocol violation that endangers subject safety will mandate discontinuation of study treatment. • An additional subgroup analysis within previously treated cohort for subjects with leptomeningeal involvement versus subjects with no leptomeningeal involvement in the previously treated cohort was planned. • Exclusion criterion 5 was changed to align with ongoing vemurafenib studies and based on recommendation from the Steering Committee. • The follow-up of chest CT for evaluation of non-cuSCC was conservatively increased from 3 to 6 months. • A statement was added to clarify that cuSCC should be reported as an SAE instead of an AE of special interest to ensure its reporting to the Health Authorities in an appropriate and timely manner. • A statement was added that available biopsies from all suspicious lesions should be sent to the study-designated central pathology laboratory to ensure available specimen blocks from any suspicious lesions (including keratoacanthoma/cuSCC or new primary melanoma) are sent to a designated central pathology laboratory for the confirmation of diagnosis. • A clarification on safety reporting due to progression of the underlying malignancy was added, stating that, “An SAE with outcome death solely due to progression of the underlying malignancy does not need to be reported as an SAE".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported