Clinical trial results:
An Open-Label, Extension (Rollover) Study of Vemurafenib in Patients With BRAF V600 Mutation-Positive Malignancies Previously Enrolled in an Antecedent Vemurafenib Protocol

Summary

EudraCT number	2012-003144-80
Trial protocol	GB BE HU DE GR NL ES FI PT IT HR FR CY
Global end of trial date	17 February 2020

Results information

Result version number	v1 (current)
This version publication date	12 November 2020
First version publication date	12 November 2020

Trial information

Trial identification

Sponsor protocol code	GO28399

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01739764
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH4070
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	17 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety of Vemurafenib

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	19 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bosnia and Herzegovina: 3
Country: Number of subjects enrolled	Belarus: 2
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Cyprus: 3
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Egypt: 12
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Korea, Republic of: 41
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Serbia: 8

Country: Number of subjects enrolled	United States: 37
Country: Number of subjects enrolled	South Africa: 5
Worldwide total number of subjects	215
EEA total number of subjects	72

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)	162
From 65 to 84 years	51
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 82 centers in 24 countries.

Pre-assignment

Screening details:

215 subjects were enrolled into this OLE study and were included in the Safety population.

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	Vemurafenib 480mg BID

Arm description:

Subjects received oral vemurafenib at 480 mg BID, depending on the last dose in the antecedent protocol until progression of disease or as long as the subject is deriving clinical benefit, as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the sponsor to terminate the study, whichever occurs first.

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

Dosage and administration details:

Vemurafenib was administered orally twice daily (BID) at a dose of 480mg.

Arm title	Vemurafenib 720mg BID

Arm description:

Subjects received oral vemurafenib at 720 mg BID, depending on the last dose in the antecedent protocol until progression of disease or as long as the subject is deriving clinical benefit, as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the sponsor to terminate the study, whichever occurs first.

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

Dosage and administration details:

Vemurafenib was administered orally twice daily (BID) at a dose of 720mg.

Arm title	Vemurafenib 960mg BID

Arm description:

Subjects received oral vemurafenib at 960 mg BID, depending on the last dose in the antecedent protocol until progression of disease or as long as the subject is deriving clinical benefit, as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the sponsor to terminate the study, whichever occurs first.

Arm type	Experimental

Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	Zelboraf
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vemurafenib was administered orally twice daily (BID) at a dose of 960mg.

Number of subjects in period 1	Vemurafenib 480mg BID	Vemurafenib 720mg BID	Vemurafenib 960mg BID
Started	29	40	146
Completed	3	4	20
Not completed	26	36	126
Adverse event, serious fatal	4	6	38
Physician decision	2	2	4
Consent withdrawn by subject	6	5	27
Non-Compliance	-	-	1
Adverse event, non-fatal	-	3	4
Progressive Disease	3	5	16
Multiple Reasons	3	2	3
Study Terminated by Sponsor	8	13	26
Lost to follow-up	-	-	5
Protocol deviation	-	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Vemurafenib 480mg BID
Reporting group description:	
Subjects received oral vemurafenib at 480 mg BID, depending on the last dose in the antecedent protocol until progression of disease or as long as the subject is deriving clinical benefit, as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the sponsor to terminate the study, whichever occurs first.	
Reporting group title	Vemurafenib 720mg BID
Reporting group description:	
Subjects received oral vemurafenib at 720 mg BID, depending on the last dose in the antecedent protocol until progression of disease or as long as the subject is deriving clinical benefit, as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the sponsor to terminate the study, whichever occurs first.	
Reporting group title	Vemurafenib 960mg BID
Reporting group description:	
Subjects received oral vemurafenib at 960 mg BID, depending on the last dose in the antecedent protocol until progression of disease or as long as the subject is deriving clinical benefit, as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the sponsor to terminate the study, whichever occurs first.	

Reporting group values	Vemurafenib 480mg BID	Vemurafenib 720mg BID	Vemurafenib 960mg BID
Number of subjects	29	40	146
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	18	22	122
From 65-84 years	10	17	24
85 years and over	1	1	0
Age Continuous			
Units: Years			
arithmetic mean	60.4	60.6	52.3
standard deviation	± 11.7	± 12.4	± 13.5
Sex: Female, Male			
Units: Participants			
Female	18	20	57
Male	11	20	89
Race/Ethnicity, Customized			
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	2	3
Not Hispanic or Latino	24	37	137
Not Stated	3	1	6
Race/Ethnicity, Customized			

Race			
Units: Subjects			
Asian	2	2	39
Black or African American	1	0	0
White	23	37	101
Other	0	1	2
Unknown	3	0	4

Reporting group values	Total		
Number of subjects	215		
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)	162		
From 65-84 years	51		
85 years and over	2		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	95		
Male	120		
Race/Ethnicity, Customized			
Ethnicity			
Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	198		
Not Stated	10		
Race/Ethnicity, Customized			
Race			
Units: Subjects			
Asian	43		
Black or African American	1		
White	161		
Other	3		
Unknown	7		

End points

End points reporting groups

Reporting group title	Vemurafenib 480mg BID

Reporting group description:

Subjects received oral vemurafenib at 480 mg BID, depending on the last dose in the antecedent protocol until progression of disease or as long as the subject is deriving clinical benefit, as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the sponsor to terminate the study, whichever occurs first.

Reporting group title	Vemurafenib 720mg BID

Reporting group description:

Subjects received oral vemurafenib at 720 mg BID, depending on the last dose in the antecedent protocol until progression of disease or as long as the subject is deriving clinical benefit, as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the sponsor to terminate the study, whichever occurs first.

Reporting group title	Vemurafenib 960mg BID

Reporting group description:

Subjects received oral vemurafenib at 960 mg BID, depending on the last dose in the antecedent protocol until progression of disease or as long as the subject is deriving clinical benefit, as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the sponsor to terminate the study, whichever occurs first.

Primary: Dose Intensity of Vemurafenib

End point title	Dose Intensity of Vemurafenib[1]

End point description:

Dose Intensity was defined as (total actual doses taken/total planned doses) *100, where total planned doses = prescribed doses * planned days on treatment, where planned days on treatment were defined as the interval between date of first dose and date of last dose. Please note that for this Outcome Measure, one subject who received 960 mg BID of Vemurafenib had no treatment end date indicated and was excluded from the calculation of study treatment exposure summaries.

End point type	Primary

End point timeframe:

Baseline up to a maximum of 7 years.

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: No statistical analyses were performed, as no efficacy analysis was conducted and only safety data was collected.

End point values	Vemurafenib 480mg BID	Vemurafenib 720mg BID	Vemurafenib 960mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	40	145	
Units: Percentage of Planned Dose				
arithmetic mean (standard deviation)	95.3 (± 8.1)	92.9 (± 12.1)	94.5 (± 11.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AEs) or Serious Adverse

Events (SAEs)

End point title	Percentage of Subjects With Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An Adverse Event can therefore be any unfavorable and unintended sign (including abnormal laboratory values or abnormal clinical test results), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as Adverse Events. Reported are the Percentage of Subjects with AEs and Serious Adverse Events (SAEs).

End point type	Secondary

End point timeframe:

Baseline up to 28 days after the last dose of study drug (up to a maximum of 7 years).

End point values	Vemurafenib 480mg BID	Vemurafenib 720mg BID	Vemurafenib 960mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	40	146	
Units: Percentage of Subjects				
number (not applicable)				
AEs	93.1	92.5	93.2	
SAEs	48.3	37.5	19.9	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days after the last dose of study drug (up to a maximum of 7 years).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Vemurafenib 480mg BID

Reporting group description:

Subjects received oral vemurafenib at 480 mg BID, depending on the last dose in the antecedent protocol until progression of disease or as long as the subject is deriving clinical benefit, as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the sponsor to terminate the study, whichever occurs first.

Reporting group title	Vemurafenib 960mg BID

Reporting group description:

Subjects received oral vemurafenib at 960 mg BID, depending on the last dose in the antecedent protocol until progression of disease or as long as the subject is deriving clinical benefit, as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the sponsor to terminate the study, whichever occurs first.

Reporting group title	Vemurafenib 720mg BID

Reporting group description:

Subjects received oral vemurafenib at 720 mg BID, depending on the last dose in the antecedent protocol until progression of disease or as long as the subject is deriving clinical benefit, as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up, or decision of the sponsor to terminate the study, whichever occurs first.

Serious adverse events	Vemurafenib 480mg BID	Vemurafenib 960mg BID	Vemurafenib 720mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 29 (48.28%)	29 / 146 (19.86%)	15 / 40 (37.50%)
number of deaths (all causes)	4	38	6
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BRAIN NEOPLASM BENIGN			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BREAST CANCER			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CEREBRAL HAEMANGIOMA			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC CANCER			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALIGNANT MELANOMA			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTASES TO LUNG			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTATIC MALIGNANT MELANOMA			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
TRACHEAL RESECTION			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEATH			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
FATIGUE			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
BRONCHOSPASM			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			

subjects affected / exposed	1 / 29 (3.45%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPISTAXIS			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOPTYSIS			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA ASPIRATION			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
ANXIETY DISORDER			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BIPOLAR DISORDER			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COMPLETED SUICIDE			

subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FEMUR FRACTURE			

subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRACHEAL HAEMORRHAGE			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTERIOSCLEROSIS CORONARY ARTERY			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 29 (3.45%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 29 (0.00%)	3 / 146 (2.05%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			

CEREBRAL INFARCTION			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPILEPSY			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FACIAL PARALYSIS			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYDROCEPHALUS			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEIZURE			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

CATARACT NUCLEAR			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAROPHTHALMIA			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
COLITIS ULCERATIVE			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	0 / 29 (0.00%)	3 / 146 (2.05%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULAR PERFORATION			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
GASTRIC ULCER			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOCHEZIA			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOPERITONEUM			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHOIDS			

subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL STENOSIS			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL HAEMORRHAGE			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
JAUNDICE			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

RENAL COLIC			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOPATHY TOXIC			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NECK PAIN			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PATHOLOGICAL FRACTURE			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ROTATOR CUFF SYNDROME			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
CELLULITIS			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ERYSIPELAS			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	1 / 29 (3.45%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SINUSITIS BACTERIAL			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

DIABETES MELLITUS			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Vemurafenib 480mg BID	Vemurafenib 960mg BID	Vemurafenib 720mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 29 (72.41%)	119 / 146 (81.51%)	29 / 40 (72.50%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 29 (0.00%)	3 / 146 (2.05%)	2 / 40 (5.00%)
occurrences (all)	0	3	4
MELANOCYTIC NAEVUS			
subjects affected / exposed	2 / 29 (6.90%)	4 / 146 (2.74%)	1 / 40 (2.50%)
occurrences (all)	4	5	2
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	0 / 29 (0.00%)	7 / 146 (4.79%)	2 / 40 (5.00%)
occurrences (all)	0	13	3
SKIN PAPILLOMA			
subjects affected / exposed	1 / 29 (3.45%)	16 / 146 (10.96%)	0 / 40 (0.00%)
occurrences (all)	1	24	0
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	2 / 29 (6.90%)	8 / 146 (5.48%)	3 / 40 (7.50%)
occurrences (all)	2	8	3
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	3 / 29 (10.34%)	3 / 146 (2.05%)	5 / 40 (12.50%)
occurrences (all)	4	3	5
FATIGUE			
subjects affected / exposed	2 / 29 (6.90%)	28 / 146 (19.18%)	5 / 40 (12.50%)
occurrences (all)	2	33	5
OEDEMA PERIPHERAL			

subjects affected / exposed	0 / 29 (0.00%)	5 / 146 (3.42%)	2 / 40 (5.00%)
occurrences (all)	0	6	2
PYREXIA			
subjects affected / exposed	1 / 29 (3.45%)	9 / 146 (6.16%)	1 / 40 (2.50%)
occurrences (all)	1	11	2
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	2 / 29 (6.90%)	10 / 146 (6.85%)	1 / 40 (2.50%)
occurrences (all)	2	10	1
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 29 (0.00%)	3 / 146 (2.05%)	2 / 40 (5.00%)
occurrences (all)	0	4	3
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	2 / 29 (6.90%)	8 / 146 (5.48%)	4 / 40 (10.00%)
occurrences (all)	2	8	9
BLOOD CHOLESTEROL INCREASED			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	2 / 40 (5.00%)
occurrences (all)	0	2	2
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	0 / 29 (0.00%)	7 / 146 (4.79%)	2 / 40 (5.00%)
occurrences (all)	0	11	2
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 29 (3.45%)	8 / 146 (5.48%)	3 / 40 (7.50%)
occurrences (all)	3	10	3
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
WEIGHT DECREASED			
subjects affected / exposed	1 / 29 (3.45%)	10 / 146 (6.85%)	1 / 40 (2.50%)
occurrences (all)	1	10	1
Injury, poisoning and procedural complications			
SUNBURN			

subjects affected / exposed	0 / 29 (0.00%)	6 / 146 (4.11%)	2 / 40 (5.00%)
occurrences (all)	0	8	2
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	2 / 29 (6.90%)	2 / 146 (1.37%)	3 / 40 (7.50%)
occurrences (all)	2	2	3
HEADACHE			
subjects affected / exposed	0 / 29 (0.00%)	15 / 146 (10.27%)	4 / 40 (10.00%)
occurrences (all)	0	15	4
NEUROPATHY PERIPHERAL			
subjects affected / exposed	2 / 29 (6.90%)	2 / 146 (1.37%)	0 / 40 (0.00%)
occurrences (all)	2	2	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 29 (3.45%)	13 / 146 (8.90%)	5 / 40 (12.50%)
occurrences (all)	1	18	6
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	3 / 40 (7.50%)
occurrences (all)	0	1	3
Eye disorders			
GLAUCOMA			
subjects affected / exposed	0 / 29 (0.00%)	0 / 146 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
UVEITIS			
subjects affected / exposed	2 / 29 (6.90%)	3 / 146 (2.05%)	2 / 40 (5.00%)
occurrences (all)	2	4	5
VISION BLURRED			
subjects affected / exposed	2 / 29 (6.90%)	1 / 146 (0.68%)	2 / 40 (5.00%)
occurrences (all)	2	1	2
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	3 / 29 (10.34%)	4 / 146 (2.74%)	4 / 40 (10.00%)
occurrences (all)	6	4	4
CONSTIPATION			
subjects affected / exposed	2 / 29 (6.90%)	6 / 146 (4.11%)	2 / 40 (5.00%)
occurrences (all)	2	7	2

ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 29 (6.90%)	2 / 146 (1.37%)	1 / 40 (2.50%)
occurrences (all)	2	2	1
DIARRHOEA			
subjects affected / exposed	3 / 29 (10.34%)	16 / 146 (10.96%)	3 / 40 (7.50%)
occurrences (all)	6	18	5
DYSPEPSIA			
subjects affected / exposed	1 / 29 (3.45%)	8 / 146 (5.48%)	3 / 40 (7.50%)
occurrences (all)	1	8	3
DYSPHAGIA			
subjects affected / exposed	2 / 29 (6.90%)	2 / 146 (1.37%)	1 / 40 (2.50%)
occurrences (all)	2	2	1
NAUSEA			
subjects affected / exposed	4 / 29 (13.79%)	16 / 146 (10.96%)	8 / 40 (20.00%)
occurrences (all)	4	22	8
VOMITING			
subjects affected / exposed	2 / 29 (6.90%)	12 / 146 (8.22%)	4 / 40 (10.00%)
occurrences (all)	2	13	5
Skin and subcutaneous tissue disorders			
ACTINIC KERATOSIS			
subjects affected / exposed	2 / 29 (6.90%)	7 / 146 (4.79%)	3 / 40 (7.50%)
occurrences (all)	2	12	3
ALOPECIA			
subjects affected / exposed	0 / 29 (0.00%)	21 / 146 (14.38%)	2 / 40 (5.00%)
occurrences (all)	0	21	2
DERMAL CYST			
subjects affected / exposed	1 / 29 (3.45%)	5 / 146 (3.42%)	2 / 40 (5.00%)
occurrences (all)	1	5	2
DERMATITIS			
subjects affected / exposed	0 / 29 (0.00%)	2 / 146 (1.37%)	2 / 40 (5.00%)
occurrences (all)	0	2	2
DRY SKIN			
subjects affected / exposed	0 / 29 (0.00%)	9 / 146 (6.16%)	5 / 40 (12.50%)
occurrences (all)	0	10	5
ERYTHEMA			

subjects affected / exposed	3 / 29 (10.34%)	7 / 146 (4.79%)	2 / 40 (5.00%)
occurrences (all)	5	13	2
HYPERKERATOSIS			
subjects affected / exposed	1 / 29 (3.45%)	20 / 146 (13.70%)	3 / 40 (7.50%)
occurrences (all)	1	21	4
PANNICULITIS			
subjects affected / exposed	2 / 29 (6.90%)	3 / 146 (2.05%)	1 / 40 (2.50%)
occurrences (all)	2	10	1
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	2 / 29 (6.90%)	12 / 146 (8.22%)	4 / 40 (10.00%)
occurrences (all)	2	13	4
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	1 / 29 (3.45%)	22 / 146 (15.07%)	2 / 40 (5.00%)
occurrences (all)	1	32	4
PRURITUS			
subjects affected / exposed	1 / 29 (3.45%)	13 / 146 (8.90%)	3 / 40 (7.50%)
occurrences (all)	1	15	3
RASH			
subjects affected / exposed	2 / 29 (6.90%)	14 / 146 (9.59%)	1 / 40 (2.50%)
occurrences (all)	2	16	1
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	4 / 29 (13.79%)	30 / 146 (20.55%)	10 / 40 (25.00%)
occurrences (all)	4	41	15
BACK PAIN			
subjects affected / exposed	1 / 29 (3.45%)	9 / 146 (6.16%)	1 / 40 (2.50%)
occurrences (all)	2	9	1
MUSCULOSKELETAL PAIN			
subjects affected / exposed	2 / 29 (6.90%)	2 / 146 (1.37%)	0 / 40 (0.00%)
occurrences (all)	2	2	0
MYALGIA			
subjects affected / exposed	0 / 29 (0.00%)	6 / 146 (4.11%)	2 / 40 (5.00%)
occurrences (all)	0	6	3
PAIN IN EXTREMITY			

subjects affected / exposed	2 / 29 (6.90%)	7 / 146 (4.79%)	2 / 40 (5.00%)
occurrences (all)	2	12	2
Infections and infestations			
CHORIORETINITIS			
subjects affected / exposed	2 / 29 (6.90%)	0 / 146 (0.00%)	1 / 40 (2.50%)
occurrences (all)	2	0	1
NASOPHARYNGITIS			
subjects affected / exposed	2 / 29 (6.90%)	10 / 146 (6.85%)	1 / 40 (2.50%)
occurrences (all)	2	10	1
GASTROENTERITIS			
subjects affected / exposed	0 / 29 (0.00%)	1 / 146 (0.68%)	2 / 40 (5.00%)
occurrences (all)	0	1	2
PNEUMONIA			
subjects affected / exposed	2 / 29 (6.90%)	2 / 146 (1.37%)	3 / 40 (7.50%)
occurrences (all)	2	2	3
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 29 (6.90%)	6 / 146 (4.11%)	1 / 40 (2.50%)
occurrences (all)	3	7	1
URINARY TRACT INFECTION			
subjects affected / exposed	3 / 29 (10.34%)	1 / 146 (0.68%)	4 / 40 (10.00%)
occurrences (all)	3	1	5
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	2 / 29 (6.90%)	19 / 146 (13.01%)	3 / 40 (7.50%)
occurrences (all)	2	24	5
DEHYDRATION			
subjects affected / exposed	2 / 29 (6.90%)	0 / 146 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2013	Following updates were made: [1] Safety Information for Vemurafenib updated to include three newly identified adverse drug reactions in subjects treated with Vemurafenib; [2] Updates to Study Title, Medical Monitor contact information, references to Urinalysis removed; [3] Clarification of timing for prohibited therapy prior to study entry; [4] Clarification to personnel who can perform dermatological examinations and [5] Updating of language around serious adverse events and adverse events of special interest.
21 March 2014	Following updates were made: [1] Updating of Safety Information for Vemurafenib; [2] Modification of oral Vemurafenib dose to include 960 mg, 720 mg and 480 mg twice daily; [3] Deletion of anticoagulation therapy and antiplatelet agents from the list of prohibited medications; [4] Addition of instructions on the collection of electrocardiograms; [5] Changes to the permitted windows of time for the screening assessments; [6] Modification to the Schedule of Assessments and [7] Change to allow for a one-year safety follow-up visit for subjects with papillary thyroid cancer.
13 March 2015	Following update was made: [1] New safety information for subjects being treated with Vemurafenib for pancreatitis and for potentiation of radiation treatment toxicity and the reporting of a second case of progression of a preexisting RAS-mutated malignancy (pancreatic adenocarcinoma with KRAS mutation).
28 August 2018	Following updates were made: [1] Removal of Safety follow-up visits at 3 and 6 months; [2] Updating of End of study safety follow up and dermatological evaluations; [3] Updating of Follow-up for new primary malignancies; [4] Addition of new Safety information; [5] Clarification to Adverse Event reporting and [6] Clarification to language on partner pregnancies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported