



Clinical trial results:

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

Summary

EudraCT number	2012-003008-11
Trial protocol	GB ES CZ AT NO DE BE SE IT NL HU FR
Global end of trial date	

Results information

Result version number	v2
This version publication date	19 May 2016
First version publication date	07 August 2015
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Error identified during QC that requires correction

Trial information

Trial identification

Sponsor protocol code	GO28141
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01689519
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 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline , F. Hoffmann-La Roche AG, 41 61 6878333, 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	Interim
Date of interim/final analysis	09 May 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of vemurafenib in combination with GDC-0973, compared with vemurafenib and placebo, in previously untreated BRAFV600 mutation-positive subjects with unresectable locally advanced or metastatic melanoma, as measured by prolongation of progression-free survival (PFS), as assessed by the study site investigator.

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	08 January 2013
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	Netherlands: 9
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 47
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Italy: 95
Country: Number of subjects enrolled	Australia: 56
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	New Zealand: 10

Worldwide total number of subjects	495
EEA total number of subjects	329

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)	362
From 65 to 84 years	128
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Written informed consent for participation in the study was obtained before performing any study-specific screening tests or evaluations.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Vemurafenib

Arm description:

Subjects received placebo orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

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

Dosage and administration details:

Placebo orally once a day on days 1-21 of each 28-day treatment cycle. Treatment will be administered until disease progression, unacceptable toxicity or withdrawal of consent.

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

Dosage and administration details:

60 mg orally twice a day on days 1-28 of each 28-day cycle. Treatment will be administered until disease progression, unacceptable toxicity or withdrawal of consent.

Arm title	Cobimetinib + Vemurafenib
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Arm description:

Subjects received cobimetinib 60 mg orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Arm type	Experimental
Investigational medicinal product name	cobimetinib
Investigational medicinal product code	
Other name	GDC-0973
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

60 mg orally once a day on days 1-21 of each 28-day treatment cycle. Treatment will be administered until disease progression, unacceptable toxicity or withdrawal of consent

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 orally twice a day on days 1-28 of each 28-day cycle. Treatment will be administered until disease progression, unacceptable toxicity or withdrawal of consent

Number of subjects in period 1	Placebo + Vemurafenib	Cobimetinib + Vemurafenib
Started	248	247
Completed	181	199
Not completed	67	48
Consent withdrawn by subject	13	10
Physician decision	-	3
Death	51	34
Lost to follow-up	3	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo + Vemurafenib
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Reporting group description:

Subjects received placebo orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Reporting group title	Cobimetinib + Vemurafenib
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Reporting group description:

Subjects received cobimetinib 60 mg orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Reporting group values	Placebo + Vemurafenib	Cobimetinib + Vemurafenib	Total
Number of subjects	248	247	495
Age categorical Units: Subjects			
< 18	0	0	0
18 - 64	179	183	362
65 - 84	68	60	128
>= 85	1	4	5
Age continuous Units: years			
arithmetic mean	55.3	54.9	
standard deviation	± 13.8	± 14	-
Gender categorical Units: Subjects			
Female	108	101	209
Male	140	146	286

End points

End points reporting groups

Reporting group title	Placebo + Vemurafenib
Reporting group description: Subjects received placebo orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.	
Reporting group title	Cobimetinib + Vemurafenib
Reporting group description: Subjects received cobimetinib 60 mg orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.	

Primary: Progression-free survival

End point title	Progression-free survival
End point description: Progression-free survival was defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using Response Evaluation Criteria in Solid Tumors v1.1, or death from any cause, whichever came first.	
End point type	Primary
End point timeframe: Baseline to the 09 May 2014 data cut-off (up to 1 year, 4 months)	

End point values	Placebo + Vemurafenib	Cobimetinib + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	247 ^[1]		
Units: months				
median (confidence interval 95%)	6.21 (5.55 to 7.39)	9.89 (9 to 999.99)		

Notes:

[1] - Upper limit of the confidence interval could not be calculated due to too few events. 999.99 = NE

Statistical analyses

Statistical analysis title	geographic region/metastasis classification
Comparison groups	Placebo + Vemurafenib v Cobimetinib + Vemurafenib
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.512

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.387
upper limit	0.679

Secondary: Overall survival

End point title	Overall survival
End point description:	
Overall survival was defined as the time from randomization until the date of death from any cause.	
End point type	Secondary
End point timeframe:	
Baseline to the 09 May 2014 data cut-off (up to 1 year, 4 months)	

End point values	Placebo + Vemurafenib	Cobimetinib + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248 ^[2]	247 ^[3]		
Units: months				
median (confidence interval 95%)	999.99 (999.99 to 999.99)	999.99 (999.99 to 999.99)		

Notes:

[2] - 999.99 = NE Not evaluable

[3] - 999.99 = NE Not evaluable

Statistical analyses

Statistical analysis title	Stratified analysis
Comparison groups	Placebo + Vemurafenib v Cobimetinib + Vemurafenib
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0463
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.645
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.417
upper limit	0.996

Secondary: Percentage of subjects with an objective response

End point title	Percentage of subjects with an objective response
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End point description:

An objective response was defined as a complete response or a partial response determined on two consecutive occasions ≥ 4 weeks apart. Responses were determined by Response Evaluation Criteria in Solid Tumors v1.1. A complete response was defined as the disappearance of all target lesions or the disappearance of all non-target lesions and normalization of tumor marker level. A partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of the longest diameter of target lesions.

End point type	Secondary
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End point timeframe:

Baseline to the 09 May 2014 data cut-off (up to 1 year, 4 months)

End point values	Placebo + Vemurafenib	Cobimetinib + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	247		
Units: percentage of participants				
number (confidence interval 95%)	44.8 (38.46 to 51.18)	67.6 (61.39 to 73.41)		

Statistical analyses

Statistical analysis title	Stratified analysis
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Statistical analysis description:

Stratified analysis by geographic region and metastasis classification (disease stage).

Comparison groups	Placebo + Vemurafenib v Cobimetinib + Vemurafenib
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Difference in ratio
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.79

Secondary: Duration of response

End point title	Duration of response
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End point description:

Duration of response was defined as the time from first occurrence of a documented confirmed objective response until the time of disease progression, as determined by investigator review of tumor assessments using Response Evaluation Criteria in Solid Tumors v1.1 or death from any cause during the study. Disease progression was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions and/or unequivocal progression of

existing non-target lesions.

End point type	Secondary
End point timeframe:	
Baseline to the 09 May 2014 data cut-off (up to 1 year, 4 months)	

End point values	Placebo + Vemurafenib	Cobimetinib + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248 ^[4]	247 ^[5]		
Units: months				
median (confidence interval 95%)	7.29 (5.78 to 999.99)	999.99 (9.3 to 999.99)		

Notes:

[4] - Upper limit of the confidence interval could not be calculated due to too few events. 999.99 = NE

[5] - Upper limit of the confidence interval could not be calculated due to too few events. 999.99 = NE

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of each subject's randomization into the study until their last visit until 28 days after the last dose of study drug or until 09 May 2014 data cut-off (up to 1 year, 4 months).

Adverse event reporting additional description:

Safety population: All subjects who received at least 1 dose of study treatment (ie, cobimetinib/placebo or vemurafenib).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Cobimetinib + Vemurafenib
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Reporting group description:

Subjects received cobimetinib 60 mg orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Reporting group title	Placebo + Vemurafenib
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Reporting group description:

Subjects received placebo orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Serious adverse events	Cobimetinib + Vemurafenib	Placebo + Vemurafenib	
Total subjects affected by serious adverse events			
subjects affected / exposed	114 / 247 (46.15%)	76 / 248 (30.65%)	
number of deaths (all causes)	6	3	
number of deaths resulting from adverse events			
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULITIS			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

ASTHENIA	subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
	occurrences causally related to treatment / all	1 / 1	0 / 0	
	deaths causally related to treatment / all	1 / 1	0 / 0	
DEATH	subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 1	0 / 0	
FATIGUE	subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
	occurrences causally related to treatment / all	1 / 1	0 / 1	
	deaths causally related to treatment / all	1 / 1	0 / 1	
MALAISE	subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
	occurrences causally related to treatment / all	1 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA	subjects affected / exposed	6 / 247 (2.43%)	3 / 248 (1.21%)	
	occurrences causally related to treatment / all	6 / 7	2 / 3	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders				
INTERSTITIAL LUNG DISEASE				
	subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
	occurrences causally related to treatment / all	1 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION				
	subjects affected / exposed	0 / 247 (0.00%)	3 / 248 (1.21%)	
	occurrences causally related to treatment / all	0 / 0	1 / 3	
	deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS				
	subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
	occurrences causally related to treatment / all	1 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	

PULMONARY EMBOLISM			
subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PULMONARY HAEMORRHAGE			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
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	3 / 247 (1.21%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 247 (1.21%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	2 / 247 (0.81%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EJECTION FRACTION DECREASED			
subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ELECTROCARDIOGRAM QT PROLONGED			

subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIPASE INCREASED			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER FUNCTION TEST ABNORMAL			
subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSAMINASES INCREASED			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	5 / 247 (2.02%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			

subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIB FRACTURE			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRAUMATIC HAEMATOMA			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER LIMB FRACTURE			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	3 / 247 (1.21%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

CARDIAC FAILURE			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
CARDIAC TAMPONADE			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDIAL EFFUSION			
subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	2 / 247 (0.81%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	2 / 247 (0.81%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONVULSION			

subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSGEUSIA			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPILEPSY			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FACIAL PARESIS			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GRAND MAL CONVULSION			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIPARESIS			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
HYDROCEPHALUS			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTRACRANIAL PRESSURE INCREASED			

subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYASTHENIA GRAVIS			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL CORD COMPRESSION			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIITH NERVE PARALYSIS			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MANIA			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
CHORIORETINOPATHY			
subjects affected / exposed	3 / 247 (1.21%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IRIDOCYCLITIS			

subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL DETACHMENT			
subjects affected / exposed	3 / 247 (1.21%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UVEITIS			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 247 (0.40%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
APHTHOUS STOMATITIS			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	3 / 247 (1.21%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULAR PERFORATION			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			

subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ANTRAL VASCULAR ECTASIA			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL PERFORATION			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	1 / 247 (0.40%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIODONTAL DISEASE			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			

subjects affected / exposed	2 / 247 (0.81%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	2 / 247 (0.81%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERSENSITIVITY			
subjects affected / exposed	3 / 247 (1.21%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DERMATITIS EXFOLIATIVE			
subjects affected / exposed	0 / 247 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS			
subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYTHEMA MULTIFORME			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYTHEMA NODOSUM			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

HYPERKERATOSIS			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANNICULITIS			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	4 / 247 (1.62%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH GENERALISED			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH MORBILLIFORM			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URTICARIA			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (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			
CALCULUS URETERIC			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL COLIC			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE ACUTE			

subjects affected / exposed	2 / 247 (0.81%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL INJURY			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHRITIS			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BURSITIS			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (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	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYALGIA			

subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PATHOLOGICAL FRACTURE			
subjects affected / exposed	2 / 247 (0.81%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POLYARTHRITIS			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RHABDOMYOLYSIS			
subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ADENOCARCINOMA OF COLON			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
BENIGN NEOPLASM			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
KERATOACANTHOMA			
subjects affected / exposed	0 / 247 (0.00%)	3 / 248 (1.21%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCINOUS BREAST CARCINOMA			

subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSITIONAL CELL CARCINOMA			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR HAEMORRHAGE			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
CELLULITIS			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL ABSCESS			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			

subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 247 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL BACTERIAL INFECTION			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	2 / 247 (0.81%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 247 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VULVAL CELLULITIS			

subjects affected / exposed	1 / 247 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cobimetinib + Vemurafenib	Placebo + Vemurafenib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	243 / 247 (98.38%)	228 / 248 (91.94%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
SEBORRHOEIC KERATOSIS			
subjects affected / exposed	9 / 247 (3.64%)	13 / 248 (5.24%)	
occurrences (all)	9	13	
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	7 / 247 (2.83%)	27 / 248 (10.89%)	
occurrences (all)	16	55	
MELANOCYTIC NAEVUS			
subjects affected / exposed	3 / 247 (1.21%)	14 / 248 (5.65%)	
occurrences (all)	3	21	
KERATOACANTHOMA			
subjects affected / exposed	2 / 247 (0.81%)	18 / 248 (7.26%)	
occurrences (all)	2	22	
SKIN PAPILLOMA			
subjects affected / exposed	11 / 247 (4.45%)	25 / 248 (10.08%)	
occurrences (all)	13	30	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	35 / 247 (14.17%)	19 / 248 (7.66%)	
occurrences (all)	40	20	
General disorders and administration site conditions			
OEDEMA PERIPHERAL			
subjects affected / exposed	27 / 247 (10.93%)	25 / 248 (10.08%)	
occurrences (all)	30	28	
FATIGUE			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CHILLS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PYREXIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ASTHENIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>82 / 247 (33.20%)</p> <p>102</p> <p>19 / 247 (7.69%)</p> <p>19</p> <p>63 / 247 (25.51%)</p> <p>81</p> <p>43 / 247 (17.41%)</p> <p>55</p>	<p>73 / 248 (29.44%)</p> <p>80</p> <p>12 / 248 (4.84%)</p> <p>14</p> <p>51 / 248 (20.56%)</p> <p>63</p> <p>33 / 248 (13.31%)</p> <p>36</p>	
<p>Respiratory, thoracic and mediastinal disorders</p> <p>OROPHARYNGEAL PAIN</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DYSPNOEA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>COUGH</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>11 / 247 (4.45%)</p> <p>11</p> <p>14 / 247 (5.67%)</p> <p>14</p> <p>18 / 247 (7.29%)</p> <p>21</p>	<p>18 / 248 (7.26%)</p> <p>24</p> <p>17 / 248 (6.85%)</p> <p>17</p> <p>26 / 248 (10.48%)</p> <p>27</p>	
<p>Psychiatric disorders</p> <p>INSOMNIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>14 / 247 (5.67%)</p> <p>16</p>	<p>18 / 248 (7.26%)</p> <p>18</p>	
<p>Investigations</p> <p>BLOOD CREATININE INCREASED</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ELECTROCARDIOGRAM QT PROLONGED</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ALANINE AMINOTRANSFERASE INCREASED</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>29 / 247 (11.74%)</p> <p>35</p> <p>9 / 247 (3.64%)</p> <p>10</p> <p>58 / 247 (23.48%)</p> <p>75</p>	<p>18 / 248 (7.26%)</p> <p>21</p> <p>12 / 248 (4.84%)</p> <p>14</p> <p>42 / 248 (16.94%)</p> <p>47</p>	

BLOOD CHOLESTEROL INCREASED			
subjects affected / exposed	13 / 247 (5.26%)	6 / 248 (2.42%)	
occurrences (all)	13	6	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	34 / 247 (13.77%)	19 / 248 (7.66%)	
occurrences (all)	35	23	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	42 / 247 (17.00%)	41 / 248 (16.53%)	
occurrences (all)	51	54	
WEIGHT DECREASED			
subjects affected / exposed	13 / 247 (5.26%)	11 / 248 (4.44%)	
occurrences (all)	13	13	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	54 / 247 (21.86%)	29 / 248 (11.69%)	
occurrences (all)	64	29	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	75 / 247 (30.36%)	7 / 248 (2.82%)	
occurrences (all)	100	7	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	19 / 247 (7.69%)	14 / 248 (5.65%)	
occurrences (all)	22	16	
EJECTION FRACTION DECREASED			
subjects affected / exposed	18 / 247 (7.29%)	6 / 248 (2.42%)	
occurrences (all)	19	7	
Injury, poisoning and procedural complications			
SUNBURN			
subjects affected / exposed	33 / 247 (13.36%)	38 / 248 (15.32%)	
occurrences (all)	39	53	
Nervous system disorders			
DYSGEUSIA			
subjects affected / exposed	33 / 247 (13.36%)	24 / 248 (9.68%)	
occurrences (all)	34	24	
HEADACHE			

subjects affected / exposed occurrences (all)	36 / 247 (14.57%) 45	35 / 248 (14.11%) 40	
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	26 / 247 (10.53%) 30	16 / 248 (6.45%) 17	
Eye disorders CHORIORETINOPATHY subjects affected / exposed occurrences (all) RETINAL DETACHMENT subjects affected / exposed occurrences (all) VISION BLURRED subjects affected / exposed occurrences (all)	27 / 247 (10.93%) 29 18 / 247 (7.29%) 21 23 / 247 (9.31%) 23	1 / 248 (0.40%) 1 0 / 248 (0.00%) 0 5 / 248 (2.02%) 5	
Gastrointestinal disorders DYSPEPSIA subjects affected / exposed occurrences (all) VOMITING subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) ABDOMINAL PAIN subjects affected / exposed occurrences (all) CONSTIPATION subjects affected / exposed occurrences (all) ABDOMINAL PAIN UPPER	17 / 247 (6.88%) 20 54 / 247 (21.86%) 75 142 / 247 (57.49%) 230 99 / 247 (40.08%) 127 23 / 247 (9.31%) 26 22 / 247 (8.91%) 23	11 / 248 (4.44%) 11 28 / 248 (11.29%) 32 67 / 248 (27.02%) 90 57 / 248 (22.98%) 66 17 / 248 (6.85%) 19 25 / 248 (10.08%) 27	

subjects affected / exposed occurrences (all)	9 / 247 (3.64%) 9	13 / 248 (5.24%) 13	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	35 / 247 (14.17%)	70 / 248 (28.23%)	
occurrences (all)	36	72	
DERMATITIS ACNEIFORM			
subjects affected / exposed	33 / 247 (13.36%)	22 / 248 (8.87%)	
occurrences (all)	40	25	
ERYTHEMA			
subjects affected / exposed	21 / 247 (8.50%)	30 / 248 (12.10%)	
occurrences (all)	30	37	
HYPERKERATOSIS			
subjects affected / exposed	26 / 247 (10.53%)	67 / 248 (27.02%)	
occurrences (all)	30	107	
ACTINIC KERATOSIS			
subjects affected / exposed	7 / 247 (2.83%)	17 / 248 (6.85%)	
occurrences (all)	12	21	
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	72 / 247 (29.15%)	38 / 248 (15.32%)	
occurrences (all)	83	42	
KERATOSIS PILARIS			
subjects affected / exposed	8 / 247 (3.24%)	22 / 248 (8.87%)	
occurrences (all)	8	23	
RASH MACULO-PAPULAR			
subjects affected / exposed	34 / 247 (13.77%)	36 / 248 (14.52%)	
occurrences (all)	53	44	
RASH			
subjects affected / exposed	96 / 247 (38.87%)	85 / 248 (34.27%)	
occurrences (all)	133	105	
PRURITUS			
subjects affected / exposed	47 / 247 (19.03%)	41 / 248 (16.53%)	
occurrences (all)	59	45	
DRY SKIN			
subjects affected / exposed	31 / 247 (12.55%)	37 / 248 (14.92%)	
occurrences (all)	33	39	

Musculoskeletal and connective tissue disorders	MYALGIA			
	subjects affected / exposed	25 / 247 (10.12%)	23 / 248 (9.27%)	
	occurrences (all)	32	25	
	MUSCULOSKELETAL PAIN			
	subjects affected / exposed	13 / 247 (5.26%)	10 / 248 (4.03%)	
	occurrences (all)	13	12	
	PAIN IN EXTREMITY			
	subjects affected / exposed	19 / 247 (7.69%)	32 / 248 (12.90%)	
Infections and infestations	occurrences (all)	24	42	
	ARTHRALGIA			
	subjects affected / exposed	83 / 247 (33.60%)	96 / 248 (38.71%)	
	occurrences (all)	114	143	
	NASOPHARYNGITIS			
	subjects affected / exposed	13 / 247 (5.26%)	9 / 248 (3.63%)	
	occurrences (all)	15	10	
	FOLLICULITIS			
Metabolism and nutrition disorders	subjects affected / exposed	14 / 247 (5.67%)	10 / 248 (4.03%)	
	occurrences (all)	14	11	
	DECREASED APPETITE			
	subjects affected / exposed	48 / 247 (19.43%)	46 / 248 (18.55%)	
	occurrences (all)	58	52	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2012	Version 2 of the protocol included the following changes: correction of typographical errors; relocation of some text and minor editing for greater clarity
24 April 2013	Version 3 of the protocol included the following changes: added PFS as assessed by independent review as a secondary endpoint; clarified exclusion criteria 4 to allow subjects with previously resected early stage melanoma into the study; added cardiac events/Grade ≥ 2 LVEF reduction as AESIs; revised guidelines for cases of emergency unblinding to allow investigators the ability to unblind without the Sponsor's approval; change in reporting windows for pregnancy and pregnant partners, for LVEF, dermatology, and ophthalmology exams after Cycle 2; revised guidelines on corrected QT interval (QTc) monitoring/cardiac consult to be more conservative; updated safety information on the cobimetinib plus vemurafenib combination; further clarified procedures described in the protocol to enhance readability and understanding; changed "GDC-0973" to "cobimetinib" throughout the document.
12 September 2013	Version 4 of the protocol included the following changes: updated safety information for consistency with the vemurafenib Investigator's Brochure; updated and further clarified procedures described in the protocol to enhance readability and understanding.
17 March 2014	Protocol Version 4 Addendum 1, In response to a request from Health Canada, the protocol was revised to include lipase and amylase testing to confirm diagnosis in suspected cases of pancreatitis. At this time, the Canadian addendum to the protocol has not been incorporated a global amendment and therefore has not been implemented globally.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported