Clinical trial results:
An Open-label, Phase II Study of Vemurafenib in Patients with BRAF V600 Mutation-positive Cancers

Summary

EudraCT number	2011-004426-10
Trial protocol	GB ES DE
Global end of trial date	27 October 2016

Results information

Result version number	v1
This version publication date	07 September 2017
First version publication date	07 September 2017

Trial information

Trial identification

Sponsor protocol code	MO28072

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01524978
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to assess the efficacy of vemurafenib in subjects with BRAF V600 mutation-positive cancers (solid tumors and multiple myeloma, except melanoma and papillary thyroid cancer) and for whom vemurafenib is deemed the best treatment option in the opinion of the 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	11 April 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 103
Country: Number of subjects enrolled	France: 63
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	208
EEA total number of subjects	105

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)	134
From 65 to 84 years	71
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

One participant with breast cancer was screened shortly after Cohort 5 (Breast Cancer) had been closed. This participant was allowed to enter the study in Cohort 7: Other BRAF V600-positive tumors. For analysis purposes Cohort 7 was split into sub-cohorts for indications with sufficient participants.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib

Arm description:

Subjects with NSCLC were treated with vemurafenib monotherapy.

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:

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm title	Cohort 2: Ovarian Cancer - vemurafenib

Arm description:

Subjects with ovarian cancer were treated with vemurafenib monotherapy.

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:

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm title	Cohort 3a: Colorectal Cancer - vemurafenib

Arm description:

Subjects with colorectal cancer were treated with vemurafenib monotherapy.

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:

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm title	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab

Arm description:

Subjects with colorectal cancer were treated with vemurafenib and cetuximab combination therapy.

Arm type	Experimental
Investigational medicinal product name	cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Escalating doses were administered on Day 1 and then once weekly by intravenous infusion. The escalating doses were as follows: Dose Level 1:300 milligrams per square meter (mg/m^2) loading dose of cetuximab and then 200 mg/m^2 weekly; Dose Level 2: 400 mg/m^2 loading dose of cetuximab and then 250 mg/m^2 weekly; Dose Level 3: 400 mg/m^2 loading dose of cetuximab and then 250 mg/m^2 weekly.

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

Dosage and administration details:

Escalating doses were given orally twice a day starting on Day 2 of Cycle 1.The escalating doses were as follows: Dose Level 1: 720 mg of vemurafenib; Dose Level 2: 720 mg of vemurafenib; Dose Level 3: 960 mg of vemurafenib.

Arm title	Cohort 4: Cholangiocarcinoma - vemurafenib

Arm description:

Subjects with cholangiocarcinoma were treated with vemurafenib monotherapy.

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:

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm title	Cohort 6: Multiple Myeloma - vemurafenib

Arm description:

Subjects with multiple myeloma were treated with vemurafenib monotherapy.

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:

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm title	Cohort 7a: ECD/LCH - vemurafenib

Arm description:

Subjects with Erdheim-Chester disease (ECD) or Langerhans cell histiocytosis (LCH) were treated with vemurafenib monotherapy.

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:

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm title	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib

Arm description:

Subjects with anaplastic thyroid cancer were treated with vemurafenib monotherapy.

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:

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm title	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib

Arm description:

Subjects with advanced stage astrocytoma were treated with vemurafenib monotherapy.

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:

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm title	Cohort 7d: Early Stage Astrocytoma - vemurafenib

Arm description:

Subjects with early stage astrocytoma were treated with vemurafenib monotherapy.

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:

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm title	Other BRAF V600-positive Tumors - vemurafenib

Arm description:

Subjects with other BRAF V600-positive tumors were treated with vemurafenib monotherapy.

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:

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

Number of subjects in period 1	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib
Started	62	4	10
Completed	0	0	0
Not completed	62	4	10
Adverse event, serious fatal	34	2	5
Consent withdrawn by subject	12	-	1
Unspecified	16	2	1
Lost to follow-up	-	-	3

Number of subjects in period 1	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab	Cohort 4: Cholangiocarcinoma - vemurafenib	Cohort 6: Multiple Myeloma - vemurafenib
Started	27	9	9
Completed	0	0	0
Not completed	27	9	9
Adverse event, serious fatal	24	4	4
Consent withdrawn by subject	1	3	1
Unspecified	2	1	3
Lost to follow-up	-	1	1

Number of subjects in period 1	Cohort 7a: ECD/LCH - vemurafenib	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib
Started	26	12	12
Completed	0	0	0
Not completed	26	12	12
Adverse event, serious fatal	1	9	5
Consent withdrawn by subject	6	2	4
Unspecified	17	1	2
Lost to follow-up	2	-	1

Number of subjects in period 1	Cohort 7d: Early Stage Astrocytoma -	Other BRAF V600-positive Tumors -

	vemurafenib	vemurafenib
Started	9	28
Completed	0	0
Not completed	9	28
Adverse event, serious fatal	6	17
Consent withdrawn by subject	-	5
Unspecified	2	5
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib
Reporting group description: Subjects with NSCLC were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 2: Ovarian Cancer - vemurafenib
Reporting group description: Subjects with ovarian cancer were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 3a: Colorectal Cancer - vemurafenib
Reporting group description: Subjects with colorectal cancer were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Reporting group description: Subjects with colorectal cancer were treated with vemurafenib and cetuximab combination therapy.	
Reporting group title	Cohort 4: Cholangiocarcinoma - vemurafenib
Reporting group description: Subjects with cholangiocarcinoma were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 6: Multiple Myeloma - vemurafenib
Reporting group description: Subjects with multiple myeloma were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 7a: ECD/LCH - vemurafenib
Reporting group description: Subjects with Erdheim-Chester disease (ECD) or Langerhans cell histiocytosis (LCH) were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib
Reporting group description: Subjects with anaplastic thyroid cancer were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib
Reporting group description: Subjects with advanced stage astrocytoma were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 7d: Early Stage Astrocytoma - vemurafenib
Reporting group description: Subjects with early stage astrocytoma were treated with vemurafenib monotherapy.	
Reporting group title	Other BRAF V600-positive Tumors - vemurafenib
Reporting group description: Subjects with other BRAF V600-positive tumors were treated with vemurafenib monotherapy.	

Reporting group values	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib
Number of subjects	62	4	10
Age categorical Units: Subjects			
Adults (18-64 years)	30	4	10
From 65-84 years	30	0	0
85 years and over	2	0	0

Age Continuous			
Units: years			
arithmetic mean	65.4	45.8	57.3
standard deviation	± 10.2	± 5.3	± 5.4
Gender, Male/Female			
Units: Subjects			
Female	27	4	5
Male	35	0	5

Reporting group values	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab	Cohort 4: Cholangiocarcinoma - vemurafenib	Cohort 6: Multiple Myeloma - vemurafenib
Number of subjects	27	9	9
Age categorical			
Units: Subjects			
Adults (18-64 years)	15	8	7
From 65-84 years	12	1	2
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	64.3	53.2	62.1
standard deviation	± 8.8	± 9.7	± 4.3
Gender, Male/Female			
Units: Subjects			
Female	18	5	3
Male	9	4	6

Reporting group values	Cohort 7a: ECD/LCH - vemurafenib	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib
Number of subjects	26	12	12
Age categorical			
Units: Subjects			
Adults (18-64 years)	15	6	12
From 65-84 years	11	6	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	60.8	66.8	41.6
standard deviation	± 13.3	± 9.2	± 12.2
Gender, Male/Female			
Units: Subjects			
Female	14	3	8
Male	12	9	4

Reporting group values	Cohort 7d: Early Stage Astrocytoma - vemurafenib	Other BRAF V600-positive Tumors - vemurafenib	Total
Number of subjects	9	28	208
Age categorical			
Units: Subjects			
Adults (18-64 years)	8	19	134

From 65-84 years	1	8	71
85 years and over	0	1	3

Age Continuous			
Units: years			
arithmetic mean	34.3	53.7	
standard deviation	± 20.7	± 17.5	-
Gender, Male/Female			
Units: Subjects			
Female	9	15	111
Male	0	13	97

End points

End points reporting groups

Reporting group title	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib
Reporting group description: Subjects with NSCLC were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 2: Ovarian Cancer - vemurafenib
Reporting group description: Subjects with ovarian cancer were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 3a: Colorectal Cancer - vemurafenib
Reporting group description: Subjects with colorectal cancer were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Reporting group description: Subjects with colorectal cancer were treated with vemurafenib and cetuximab combination therapy.	
Reporting group title	Cohort 4: Cholangiocarcinoma - vemurafenib
Reporting group description: Subjects with cholangiocarcinoma were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 6: Multiple Myeloma - vemurafenib
Reporting group description: Subjects with multiple myeloma were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 7a: ECD/LCH - vemurafenib
Reporting group description: Subjects with Erdheim-Chester disease (ECD) or Langerhans cell histiocytosis (LCH) were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib
Reporting group description: Subjects with anaplastic thyroid cancer were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib
Reporting group description: Subjects with advanced stage astrocytoma were treated with vemurafenib monotherapy.	
Reporting group title	Cohort 7d: Early Stage Astrocytoma - vemurafenib
Reporting group description: Subjects with early stage astrocytoma were treated with vemurafenib monotherapy.	
Reporting group title	Other BRAF V600-positive Tumors - vemurafenib
Reporting group description: Subjects with other BRAF V600-positive tumors were treated with vemurafenib monotherapy.	

Primary: Confirmed Best Overall Response Rate (BORR)

End point title	Confirmed Best Overall Response Rate (BORR)[1]

End point description:

Confirmed BORR: percentage of subjects with an objective response (OR) (complete response [CR], partial response [PR], stringent CR [sCR] or very good PR [VGPR]) on 2 occasions >/= 4 weeks apart as assessed by the Investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. or International Myeloma Working Group (IMWG) criteria. RECIST v1.1: CR: disappearance of all target lesions; PR: >/= 30% decrease in the sum of diameters of target lesions. IMWG: CR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and </= 5% plasma cells in bone marrow; PR: >/= 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >/= 90% or to <200 mg per 24 hours. VGPR: serum and urine M-protein detectable by immunofixation but not on electrophoresis or >/= 90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hour; sCR: CR plus normal free light chain (FLC) ratio and no

clonal cells in bone marrow.

End point type	Primary

End point timeframe:

Up to approximately 3 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: Primary efficacy results were summarized by cohort each representing specific cancer types. No statistical analyses were done, since all cohorts received vemurafenib treatment.

End point values	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[2]	0[3]	10	27
Units: percentage of subjects				
number (confidence interval 95%)	37.1 (25.16 to 50.31)	(to)	0 (0 to 30.85)	7.4 (0.91 to 24.29)

Notes:

[2] - Intent-to-Treat (ITT) population included all subjects enrolled in the study.

[3] - Efficacy analysis was not conducted if less than 7 subjects were enrolled.

End point values	Cohort 4: Cholangiocarcinoma - vemurafenib	Cohort 6: Multiple Myeloma - vemurafenib	Cohort 7a: ECD/LCH - vemurafenib	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	26	12
Units: percentage of subjects				
number (confidence interval 95%)	22.2 (2.81 to 60.01)	22.2 (2.81 to 60.01)	61.5 (40.57 to 79.77)	25 (5.49 to 57.19)

End point values	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib	Cohort 7d: Early Stage Astrocytoma - vemurafenib	Other BRAF V600-positive Tumors - vemurafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	9	0[4]	
Units: percentage of subjects				
number (confidence interval 95%)	16.7 (2.09 to 48.41)	33.3 (7.49 to 70.07)	(to)	

Notes:

[4] - Efficacy analysis was not conducted if less than 7 subjects of same cancer type were enrolled.

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed Clinical Benefit Rate (CBR)

End point title	Confirmed Clinical Benefit Rate (CBR)

End point description:

Confirmed clinical benefit rate: percentage of participants with confirmed PR or CR or Stable Disease (SD) that have lasted at least 6 months according to RECIST v1.1 or confirmed CR, PR, VGPR, sCR or SD for at least 6 months according to IMWG criteria. RECIST v1.1: PR: >/= 30% decrease in the sum of diameters of target lesions; CR: disappearance of all target lesions; SD: not meeting criteria for CR, PR or progressive disease (PD). IMWG: CR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and </= 5% plasma cells in bone marrow; PR: >/= 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >/= 90% or to <200 mg per 24 hours. VGPR: serum and urine M-protein detectable by immunofixation but not on electrophoresis or >/= 90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hour; sCR: CR plus normal FLC ratio and no clonal cells in bone marrow; SD: not meeting criteria for CR, VGPR, PR or PD.

End point type	Secondary

End point timeframe:

Up to approximately 3 years

End point values	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[5]	0[6]	10	27
Units: percentage of subjects				
number (confidence interval 95%)	48.4 (35.5 to 61.44)	(to)	0 (-9999 to 9999)	18.5 (6.3 to 38.08)

Notes:

[5] - ITT population included all subjects enrolled in the study. -9999 or 9999 = not estimable

[6] - Efficacy analysis was not conducted if less than 7 subjects were enrolled.

End point values	Cohort 4: Cholangiocarcinoma - vemurafenib	Cohort 6: Multiple Myeloma - vemurafenib	Cohort 7a: ECD/LCH - vemurafenib	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	26	12
Units: percentage of subjects				
number (confidence interval 95%)	44.4 (13.7 to 78.8)	22.2 (2.81 to 60.01)	76.9 (56.35 to 91.03)	25 (5.49 to 57.19)

End point values	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib	Cohort 7d: Early Stage Astrocytoma - vemurafenib	Other BRAF V600-positive Tumors - vemurafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	9	0[7]	
Units: percentage of subjects				
number (confidence interval 95%)	33.3 (9.92 to 65.11)	44.4 (13.7 to 78.8)	(to)	

Notes:

[7] - Efficacy analysis was not conducted if less than 7 subjects of same cancer type were enrolled.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR: percentage of subjects with an objective response (OR) (CR, PR, sCR or VGPR) on 2 occasions >/= 4 weeks apart as assessed by the Investigator using RECIST v1.1. or IMWG criteria. RECIST v1.1: CR: disappearance of all target lesions; PR: >/= 30% decrease in the sum of diameters of target lesions. IMWG: CR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and </= 5% plasma cells in bone marrow; PR: >/= 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >/= 90% or to <200 mg per 24 hours. VGPR: serum and urine M-protein detectable by immunofixation but not on electrophoresis or >/= 90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hour; sCR: CR plus normal free light chain (FLC) ratio and no clonal cells in bone marrow. 9999 or -9999=N/A= not applicable

End point type	Secondary

End point timeframe:

Up to approximately 3 years

End point values	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[8]	0[9]	10	27
Units: percentage of subjects				
number (confidence interval 95%)				
CR	0 (0 to 5.78)	(to)	0 (0 to 30.85)	0 (0 to 12.77)
PR	37.1 (25.16 to 50.31)	(to)	0 (0 to 30.85)	7.4 (0.91 to 24.29)
VGPR	9999 (-9999 to 9999)	(to)	9999 (-9999 to 9999)	9999 (-9999 to 9999)
sCR	9999 (-9999 to 9999)	(to)	9999 (-9999 to 9999)	9999 (-9999 to 9999)

Notes:

[8] - ITT population included all subjects enrolled in the study.

[9] - Efficacy analysis was not conducted if less than 7 subjects were enrolled.

End point values	Cohort 4: Cholangiocarcinoma - vemurafenib	Cohort 6: Multiple Myeloma - vemurafenib	Cohort 7a: ECD/LCH - vemurafenib	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	26	12
Units: percentage of subjects				
number (confidence interval 95%)				
CR	0 (0 to 33.63)	0 (0 to 33.63)	7.7 (0.95 to 25.13)	8.3 (0.21 to 38.48)
PR	22.2 (2.81 to 60.01)	11.1 (0.28 to 48.25)	53.8 (33.37 to 73.41)	16.7 (2.09 to 48.41)
VGPR	9999 (-9999 to 9999)	11.1 (0.28 to 48.25)	9999 (-9999 to 9999)	9999 (-9999 to 9999)
sCR	9999 (-9999 to 9999)	0 (0 to 33.63)	9999 (-9999 to 9999)	9999 (-9999 to 9999)

End point values	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib	Cohort 7d: Early Stage Astrocytoma - vemurafenib	Other BRAF V600-positive Tumors - vemurafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	9	0[10]	
Units: percentage of subjects				
number (confidence interval 95%)				
CR	8.3 (0.21 to 38.48)	0 (0 to 33.63)	(to)	
PR	8.3 (0.21 to 38.48)	33.3 (7.49 to 70.07)	(to)	
VGPR	9999 (-9999 to 9999)	9999 (-9999 to 9999)	(to)	
sCR	9999 (-9999 to 9999)	9999 (-9999 to 9999)	(to)	

Notes:

[10] - Efficacy analysis was not conducted if less than 7 subjects of same cancer type were enrolled.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was defined as the period from the date of initial PR or CR for solid tumors according to RECISTv1.1 and CR, PR, VGPR or sCR for multiple myeloma according to IMWG criteria, until the date of PD or death from any cause. RECIST v1.1: PD: At least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. IMWG: PD: increase of >/= 25% from lowest response value in serum or urine M-protein or bone marrow plasma cell percentage or development of new or increase in size of bone lesions or soft tissue plasmacytomas. ITT population included all subjects enrolled in the study irrespective of whether they had received study medication or not. 9999 = not estimable

End point type	Secondary

End point timeframe:

Up to approximately 3 years

End point values	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	0[11]	0[12]	2
Units: months				
median (confidence interval 95%)	7.16 (5.49 to 18.43)	(to)	(to)	6.54 (5.68 to 7.39)

Notes:

[11] - Efficacy analysis was not conducted if less than 7 subjects were enrolled.

[12] - None of the subjects had a response and therefore, duration of response could not be determined.

End point values	Cohort 4: Cholangiocarcinoma - vemurafenib	Cohort 6: Multiple Myeloma - vemurafenib	Cohort 7a: ECD/LCH - vemurafenib	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	16	3
Units: months				
median (confidence interval 95%)	12.86 (3.58 to 22.14)	9999 (9999 to 9999)	9999 (9999 to 9999)	9.95 (8.31 to 30.98)

End point values	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib	Cohort 7d: Early Stage Astrocytoma - vemurafenib	Other BRAF V600-positive Tumors - vemurafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	3	0[13]	
Units: months				
median (confidence interval 95%)	9999 (13.08 to 9999)	3.42 (2.4 to 7.49)	(to)	

Notes:

[13] - Efficacy analysis was not conducted if less than 7 subjects of same cancer type were enrolled.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was defined as the time from the first day of study treatment to the date of first CR, or PR for solid tumors according to RECISTv1.1 and CR, PR, VGPR or sCR for multiple myeloma according to IMWG criteria. RECIST v1.1: CR: disappearance of all target lesions; PR: at least a 30% decrease in the sum of diameters of target lesions. IMWG criteria: CR: negative immunofixation on serum and urine and disappearance of any soft tissue plasmacytomas and </= 5% plasma cells in bone marrow; PR: >/= 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >/= 90% or to < 200 mg per 24 hours. VGPR: serum and urine M-protein detectable by immunofixation but not on electrophoresis or >/= 90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hour; sCR: CR plus normal FLC ratio and no clonal cells in bone marrow. ITT population included all subjects enrolled in the study. -9999 or 9999 = not estimable

End point type	Secondary

End point timeframe:

Up to approximately 3 years

End point values	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	0[14]	10	27
Units: months				
median (confidence interval 95%)	7.26 (3.68 to 9999)	(to)	9999 (-9999 to 9999)	9999 (-9999 to 9999)

Notes:

[14] - Efficacy analysis was not conducted if less than 7 subjects were enrolled.

End point values	Cohort 4: Cholangiocarcinoma - vemurafenib	Cohort 6: Multiple Myeloma - vemurafenib	Cohort 7a: ECD/LCH - vemurafenib	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	26	12
Units: months				
median (confidence interval 95%)	9999 (3.52 to 9999)	5.75 (-9999 to 9999)	5.49 (3.68 to 13.73)	9999 (1.68 to 9999)

End point values	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib	Cohort 7d: Early Stage Astrocytoma - vemurafenib	Other BRAF V600-positive Tumors - vemurafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	9	0[15]	
Units: months				
median (confidence interval 95%)	9999 (1.74 to 9999)	9999 (2.33 to 9999)	(to)	

Notes:

[15] - Efficacy analysis was not conducted if less than 7 subjects of same cancer type were enrolled.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Progression (TTP)

End point title	Time to Tumor Progression (TTP)

End point description:

TTP was defined as time from the first day of study treatment to the first occurrence of progressive disease (PD). RECIST v1.1: PD: at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. IMWG: PD: increase of >/= 25% from lowest response value in serum or urine M-protein or bone marrow plasma cell percentage or development of new or increase in size of bone lesions or soft tissue plasmacytomas. ITT population included all subjects enrolled in the study irrespective of whether they had received study medication or not. 9999 = not estimable

End point type	Secondary

End point timeframe:

Up to approximately 3 years

End point values	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	0[16]	10	27
Units: months				
median (confidence interval 95%)	7.33 (5.29 to 9.66)	(to)	3.88 (1.84 to 5.52)	3.68 (3.45 to 5.39)

Notes:

[16] - Efficacy analysis was not conducted if less than 7 subjects were enrolled.

End point values	Cohort 4: Cholangiocarcinoma - vemurafenib	Cohort 6: Multiple Myeloma - vemurafenib	Cohort 7a: ECD/LCH - vemurafenib	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	26	12
Units: months				
median (confidence interval 95%)	3.02 (1.64 to 9)	4.63 (2.89 to 9999)	9999 (9999 to 9999)	2.83 (1.77 to 5.49)

End point values	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib	Cohort 7d: Early Stage Astrocytoma - vemurafenib	Other BRAF V600-positive Tumors - vemurafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	9	0[17]	
Units: months				
median (confidence interval 95%)	5.62 (1.81 to 14.85)	5.36 (3.02 to 9.1)	(to)	

Notes:

[17] - Efficacy analysis was not conducted if less than 7 subjects of same cancer type were enrolled.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free Survival (PFS)

End point title	Progression free Survival (PFS)

End point description:

PFS was defined as the time from the first day of study treatment, until the first documented PD or death from any cause, whichever occurs first. RECIST v1.1: PD: at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. IMWG criteria: PD: increase of >/= 25% from lowest response value in serum or urine M-protein or bone marrow plasma cell percentage or development of new or increase in size of bone lesions or soft tissue plasmacytomas. ITT population included all subjects enrolled in the study irrespective of whether they had received study medication or not. 9999 = not estimable

End point type	Secondary

End point timeframe:

Up to approximately 3 years

End point values	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	0[18]	10	27
Units: months				
median (confidence interval 95%)	6.51 (5.16 to 8.97)	(to)	3.88 (1.84 to 5.52)	3.68 (1.81 to 5.39)

Notes:

[18] - Efficacy analysis was not conducted if less than 7 subjects were enrolled.

End point values	Cohort 4: Cholangiocarcinoma - vemurafenib	Cohort 6: Multiple Myeloma - vemurafenib	Cohort 7a: ECD/LCH - vemurafenib	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	26	12
Units: months				
median (confidence interval 95%)	3.02 (1.64 to 9)	4.63 (2.89 to 9999)	9999 (9999 to 9999)	2.83 (1.77 to 5.49)

End point values	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib	Cohort 7d: Early Stage Astrocytoma - vemurafenib	Other BRAF V600-positive Tumors - vemurafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	9	0[19]	
Units: months				
median (confidence interval 95%)	9.59 (1.81 to 14.78)	5.26 (3.02 to 5.72)	(to)	

Notes:

[19] - Efficacy analysis was not conducted if less than 7 subjects of same cancer type were enrolled.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as time between the first day of study treatment and date of death of any cause. ITT population included all subjects enrolled in the study irrespective of whether they had received study medication or not. 9999 = not estimable

End point type	Secondary

End point timeframe:

Up to approximately 3 years

End point values	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	0[20]	10	27
Units: months				
median (confidence interval 95%)	15.38 (9.56 to 22.77)	(to)	9.3 (7.82 to 12.88)	7.16 (5.49 to 11.73)

Notes:

[20] - Efficacy analysis was not conducted if less than 7 subjects were enrolled.

End point values	Cohort 4: Cholangiocarcinoma - vemurafenib	Cohort 6: Multiple Myeloma - vemurafenib	Cohort 7a: ECD/LCH - vemurafenib	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	26	12
Units: months				
median (confidence interval 95%)	17.94 (11.2 to 9999)	24.54 (4.96 to 9999)	9999 (9999 to 9999)	5.88 (2.17 to 16.79)

End point values	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib	Cohort 7d: Early Stage Astrocytoma - vemurafenib	Other BRAF V600-positive Tumors - vemurafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	9	0[21]	
Units: months				
median (confidence interval 95%)	40.11 (9.59 to 40.11)	12.75 (6.7 to 9999)	(to)	

Notes:

[21] - Efficacy analysis was not conducted if less than 7 subjects of same cancer type were enrolled.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Tolerated Dose for Vemurafenib in Combination with Cetuximab

End point title	Maximum Tolerated Dose for Vemurafenib in Combination with Cetuximab

End point description:

Cohort 3b included subjects with colorectal cancer treated with escalating doses of vemurafenib and

cetuximab. The escalating doses were as follows: Dose Level 1: 720 milligrams (mg) of vemurafenib orally twice daily starting on Day 2 of Cycle 1 and 300 milligrams per square meter (mg/m^2) loading dose of cetuximab by infusion and then 200 mg/m^2 weekly; Dose Level 2: 720 mg of vemurafenib twice daily starting on Day 2 of Cycle 1 and 400 mg/m^2 loading dose of cetuximab and then 250 mg/m^2 weekly; Dose Level 3: 960 mg of vemurafenib twice daily starting on Day 2 of Cycle 1 and 400 mg/m^2 loading dose of cetuximab and then 250 mg/m^2 weekly. Reported here are the maximum tolerated doses for each vemurafenib and cetuximab. The safety population included all subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to approximately 3 years

End point values	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[22]	0[23]	0[24]	14
Units: milligrams (mg)				
vemurafenib				960
cetuximab				400

Notes:

[22] - Endpoint only applies to combination therapy in cohort 3b.

[23] - Endpoint only applies to combination therapy in cohort 3b.

[24] - Endpoint only applies to combination therapy in cohort 3b.

End point values	Cohort 4: Cholangiocarcinoma - vemurafenib	Cohort 6: Multiple Myeloma - vemurafenib	Cohort 7a: ECD/LCH - vemurafenib	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[25]	0[26]	0[27]	0[28]
Units: milligrams (mg)				
vemurafenib				
cetuximab				

Notes:

[25] - Endpoint only applies to combination therapy in cohort 3b.

[26] - Endpoint only applies to combination therapy in cohort 3b.

[27] - Endpoint only applies to combination therapy in cohort 3b.

[28] - Endpoint only applies to combination therapy in cohort 3b.

End point values	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib	Cohort 7d: Early Stage Astrocytoma - vemurafenib	Other BRAF V600-positive Tumors - vemurafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[29]	0[30]	0[31]	
Units: milligrams (mg)				
vemurafenib				
cetuximab				

Notes:

[29] - Endpoint only applies to combination therapy in cohort 3b.

[30] - Endpoint only applies to combination therapy in cohort 3b.

[31] - Endpoint only applies to combination therapy in cohort 3b.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Dose-limiting Toxicities of Vemurafenib in Combination with Cetuximab

End point title	Number of Dose-limiting Toxicities of Vemurafenib in Combination with Cetuximab

End point description:

Cohort 3b included subjects with colorectal cancer treated with escalating doses of vemurafenib and cetuximab. The escalating doses were as follows: Dose Level 1: 720 milligrams (mg) of vemurafenib orally twice daily starting on Day 2 of Cycle 1 and 300 milligrams per square meter (mg/m^2) loading dose of cetuximab by infusion and then 200 mg/m^2 weekly; Dose Level 2: 720 mg of vemurafenib twice daily starting on Day 2 of Cycle 1 and 400 mg/m^2 loading dose of cetuximab and then 250 mg/m^2 weekly; Dose Level 3: 960 mg of vemurafenib twice daily starting on Day 2 of Cycle 1 and 400 mg/m^2 loading dose of cetuximab and then 250 mg/m^2 weekly. Reported here are type and number of dose limited toxicities observed. The safety population included all subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to 28 days

End point values	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[32]	0[33]	0[34]	14
Units: dose-limiting toxicities				
Grade 3 amylase increased				1
Grade 4 lipase increased				1

Notes:

[32] - Endpoint only applies to combination therapy in cohort 3b.

[33] - Endpoint only applies to combination therapy in cohort 3b.

[34] - Endpoint only applies to combination therapy in cohort 3b.

End point values	Cohort 4: Cholangiocarcinoma - vemurafenib	Cohort 6: Multiple Myeloma - vemurafenib	Cohort 7a: ECD/LCH - vemurafenib	Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[35]	0[36]	0[37]	0[38]
Units: dose-limiting toxicities				
Grade 3 amylase increased				
Grade 4 lipase increased				

Notes:

[35] - Endpoint only applies to combination therapy in cohort 3b.

[36] - Endpoint only applies to combination therapy in cohort 3b.

[37] - Endpoint only applies to combination therapy in cohort 3b.

[38] - Endpoint only applies to combination therapy in cohort 3b.

End point values	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib	Cohort 7d: Early Stage Astrocytoma - vemurafenib	Other BRAF V600-positive Tumors - vemurafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[39]	0[40]	0[41]	
Units: dose-limiting toxicities				
Grade 3 amylase increased Grade 4 lipase increased				

Notes:

[39] - Endpoint only applies to combination therapy in cohort 3b.

[40] - Endpoint only applies to combination therapy in cohort 3b.

[41] - Endpoint only applies to combination therapy in cohort 3b.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Percentage of Subjects with Adverse Event

End point title	Safety: Percentage of Subjects with Adverse Event

End point description:

An adverse event is any untoward medical occurrence in a subject 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 an abnormal laboratory finding, for example), 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. The safety population included all subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to approximately 3 years

End point values	Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib	Cohort 2: Ovarian Cancer - vemurafenib	Cohort 3a: Colorectal Cancer - vemurafenib	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	4	10	27
Units: percentage of subjects				
number (not applicable)	100	100	100	100

End point values	Cohort 4: Cholangiocarci	Cohort 6: Multiple	Cohort 7a: ECD/LCH -	Cohort 7b: Anaplastic

	noma - vemurafenib	Myeloma - vemurafenib	vemurafenib	Thyroid Cancer - vemurafenib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	26	12
Units: percentage of subjects				
number (not applicable)	100	100	100	91.7

End point values	Cohort 7c: Advanced Stage Astrocytoma - vemurafenib	Cohort 7d: Early Stage Astrocytoma - vemurafenib	Other BRAF V600-positive Tumors - vemurafenib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	9	28	
Units: percentage of subjects				
number (not applicable)	100	100	100	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline up to approximately 3 years	
Adverse event reporting additional description:	
The safety population included all subjects who received at least one dose of study medication.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab
Reporting group description:	
Subjects with colorectal cancer were treated with vemurafenib and cetuximab combination therapy.	
Reporting group title	Pooled arm - vemurafenib
Reporting group description:	
Subjects with a variety of cancer types, who were treated with vemurafenib monotherapy, were combined into this arm.	

Serious adverse events	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab	Pooled arm - vemurafenib	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 27 (40.74%)	91 / 181 (50.28%)	
number of deaths (all causes)	25	87	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	3 / 27 (11.11%)	25 / 181 (13.81%)	
occurrences causally related to treatment / all	3 / 3	38 / 39	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	2 / 27 (7.41%)	18 / 181 (9.94%)	
occurrences causally related to treatment / all	2 / 2	28 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 27 (3.70%)	7 / 181 (3.87%)	
occurrences causally related to treatment / all	1 / 1	11 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	

Squamous cell carcinoma			
subjects affected / exposed	1 / 27 (3.70%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 27 (0.00%)	4 / 181 (2.21%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myelomonocytic leukaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraganglion neoplasm			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 27 (3.70%)	2 / 181 (1.10%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 27 (0.00%)	2 / 181 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			

subjects affected / exposed	0 / 27 (0.00%)	2 / 181 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary thrombosis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 27 (0.00%)	3 / 181 (1.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 27 (0.00%)	3 / 181 (1.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Respiratory failure			
subjects affected / exposed	0 / 27 (0.00%)	2 / 181 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Laryngeal dyspnoea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 27 (3.70%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			

subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 27 (0.00%)	2 / 181 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 181 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dressler's syndrome			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
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	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Aphasia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Pseudolymphoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Iridocyclitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 27 (3.70%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
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 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastric ulcer			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 27 (3.70%)	4 / 181 (2.21%)	
occurrences causally related to treatment / all	0 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder dilatation			
subjects affected / exposed	1 / 27 (3.70%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 27 (3.70%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 27 (0.00%)	5 / 181 (2.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 27 (0.00%)	6 / 181 (3.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infection			
subjects affected / exposed	0 / 27 (0.00%)	4 / 181 (2.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchitis			
subjects affected / exposed	0 / 27 (0.00%)	3 / 181 (1.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 27 (0.00%)	2 / 181 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			

subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glucose tolerance impaired			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 27 (0.00%)	3 / 181 (1.66%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab	Pooled arm - vemurafenib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 27 (96.30%)	177 / 181 (97.79%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	3	0	
Melanocytic naevus			
subjects affected / exposed	4 / 27 (14.81%)	41 / 181 (22.65%)	
occurrences (all)	4	67	
Seborrhoeic keratosis			
subjects affected / exposed	3 / 27 (11.11%)	36 / 181 (19.89%)	
occurrences (all)	3	49	
Skin papilloma			
subjects affected / exposed	7 / 27 (25.93%)	50 / 181 (27.62%)	
occurrences (all)	8	86	
Papilloma			
subjects affected / exposed	0 / 27 (0.00%)	17 / 181 (9.39%)	
occurrences (all)	0	21	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 27 (11.11%)	28 / 181 (15.47%)	
occurrences (all)	3	38	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Asthenia			
subjects affected / exposed	10 / 27 (37.04%)	39 / 181 (21.55%)	
occurrences (all)	13	44	
Chills			
subjects affected / exposed	2 / 27 (7.41%)	10 / 181 (5.52%)	
occurrences (all)	2	10	
Fatigue			

subjects affected / exposed	6 / 27 (22.22%)	60 / 181 (33.15%)	
occurrences (all)	8	68	
Oedema peripheral			
subjects affected / exposed	4 / 27 (14.81%)	21 / 181 (11.60%)	
occurrences (all)	4	25	
Pyrexia			
subjects affected / exposed	5 / 27 (18.52%)	26 / 181 (14.36%)	
occurrences (all)	11	30	
Cyst			
subjects affected / exposed	0 / 27 (0.00%)	21 / 181 (11.60%)	
occurrences (all)	0	26	
Xerosis			
subjects affected / exposed	0 / 27 (0.00%)	16 / 181 (8.84%)	
occurrences (all)	0	18	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 27 (7.41%)	31 / 181 (17.13%)	
occurrences (all)	4	42	
Dysphonia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Dyspnoea			
subjects affected / exposed	5 / 27 (18.52%)	22 / 181 (12.15%)	
occurrences (all)	7	27	
Nasal congestion			
subjects affected / exposed	0 / 27 (0.00%)	10 / 181 (5.52%)	
occurrences (all)	0	11	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 27 (11.11%)	10 / 181 (5.52%)	
occurrences (all)	5	10	
Anxiety			
subjects affected / exposed	2 / 27 (7.41%)	14 / 181 (7.73%)	
occurrences (all)	2	14	
Insomnia			

subjects affected / exposed	0 / 27 (0.00%)	18 / 181 (9.94%)	
occurrences (all)	0	19	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 27 (7.41%)	15 / 181 (8.29%)	
occurrences (all)	2	15	
Amylase increased			
subjects affected / exposed	6 / 27 (22.22%)	0 / 181 (0.00%)	
occurrences (all)	6	0	
Blood bilirubin increased			
subjects affected / exposed	3 / 27 (11.11%)	10 / 181 (5.52%)	
occurrences (all)	3	14	
Electrocardiogram QT prolonged			
subjects affected / exposed	4 / 27 (14.81%)	37 / 181 (20.44%)	
occurrences (all)	4	52	
Lipase increased			
subjects affected / exposed	9 / 27 (33.33%)	10 / 181 (5.52%)	
occurrences (all)	10	21	
Lymphocyte count decreased			
subjects affected / exposed	3 / 27 (11.11%)	0 / 181 (0.00%)	
occurrences (all)	6	0	
Weight decreased			
subjects affected / exposed	6 / 27 (22.22%)	20 / 181 (11.05%)	
occurrences (all)	6	20	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 27 (0.00%)	15 / 181 (8.29%)	
occurrences (all)	0	17	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 27 (0.00%)	11 / 181 (6.08%)	
occurrences (all)	0	12	
Blood creatinine increased			
subjects affected / exposed	0 / 27 (0.00%)	19 / 181 (10.50%)	
occurrences (all)	0	26	
Injury, poisoning and procedural complications			

Sunburn			
subjects affected / exposed	4 / 27 (14.81%)	22 / 181 (12.15%)	
occurrences (all)	4	27	
Fall			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 27 (14.81%)	26 / 181 (14.36%)	
occurrences (all)	5	30	
Dysgeusia			
subjects affected / exposed	0 / 27 (0.00%)	24 / 181 (13.26%)	
occurrences (all)	0	25	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 27 (0.00%)	27 / 181 (14.92%)	
occurrences (all)	0	27	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 27 (11.11%)	30 / 181 (16.57%)	
occurrences (all)	3	40	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 27 (0.00%)	11 / 181 (6.08%)	
occurrences (all)	0	11	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 27 (44.44%)	12 / 181 (6.63%)	
occurrences (all)	18	13	
Abdominal pain upper			
subjects affected / exposed	4 / 27 (14.81%)	0 / 181 (0.00%)	
occurrences (all)	4	0	
Constipation			
subjects affected / exposed	5 / 27 (18.52%)	26 / 181 (14.36%)	
occurrences (all)	6	30	
Diarrhoea			
subjects affected / exposed	13 / 27 (48.15%)	49 / 181 (27.07%)	
occurrences (all)	30	67	

Dyspepsia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	3	0	
Flatulence			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	5	0	
Nausea			
subjects affected / exposed	9 / 27 (33.33%)	54 / 181 (29.83%)	
occurrences (all)	13	80	
Rectal haemorrhage			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	3	0	
Stomatitis			
subjects affected / exposed	4 / 27 (14.81%)	19 / 181 (10.50%)	
occurrences (all)	5	20	
Vomiting			
subjects affected / exposed	8 / 27 (29.63%)	41 / 181 (22.65%)	
occurrences (all)	10	55	
Dry mouth			
subjects affected / exposed	0 / 27 (0.00%)	12 / 181 (6.63%)	
occurrences (all)	0	16	
Dysphagia			
subjects affected / exposed	0 / 27 (0.00%)	14 / 181 (7.73%)	
occurrences (all)	0	16	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 27 (0.00%)	11 / 181 (6.08%)	
occurrences (all)	0	14	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	4 / 27 (14.81%)	28 / 181 (15.47%)	
occurrences (all)	4	51	
Alopecia			
subjects affected / exposed	2 / 27 (7.41%)	57 / 181 (31.49%)	
occurrences (all)	2	58	
Dermatitis acneiform			

subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Dermatitis bullous			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Dry skin			
subjects affected / exposed	2 / 27 (7.41%)	39 / 181 (21.55%)	
occurrences (all)	2	42	
Erythema			
subjects affected / exposed	7 / 27 (25.93%)	24 / 181 (13.26%)	
occurrences (all)	11	34	
Hyperkeratosis			
subjects affected / exposed	4 / 27 (14.81%)	58 / 181 (32.04%)	
occurrences (all)	9	102	
Photosensitivity reaction			
subjects affected / exposed	5 / 27 (18.52%)	39 / 181 (21.55%)	
occurrences (all)	5	44	
Pruritus			
subjects affected / exposed	5 / 27 (18.52%)	42 / 181 (23.20%)	
occurrences (all)	5	47	
Rash			
subjects affected / exposed	10 / 27 (37.04%)	44 / 181 (24.31%)	
occurrences (all)	16	60	
Rash generalised			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Toxic skin eruption			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Skin fissures			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular			
subjects affected / exposed	3 / 27 (11.11%)	42 / 181 (23.20%)	
occurrences (all)	5	59	
Dermal cyst			

subjects affected / exposed	0 / 27 (0.00%)	18 / 181 (9.94%)	
occurrences (all)	0	24	
Dermatitis			
subjects affected / exposed	0 / 27 (0.00%)	10 / 181 (5.52%)	
occurrences (all)	0	10	
Keratosis pilaris			
subjects affected / exposed	0 / 27 (0.00%)	33 / 181 (18.23%)	
occurrences (all)	0	33	
Milia			
subjects affected / exposed	0 / 27 (0.00%)	16 / 181 (8.84%)	
occurrences (all)	0	18	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 27 (0.00%)	48 / 181 (26.52%)	
occurrences (all)	0	57	
Rash papular			
subjects affected / exposed	0 / 27 (0.00%)	21 / 181 (11.60%)	
occurrences (all)	0	26	
Papule			
subjects affected / exposed	0 / 27 (0.00%)	13 / 181 (7.18%)	
occurrences (all)	0	18	
Skin lesion			
subjects affected / exposed	0 / 27 (0.00%)	11 / 181 (6.08%)	
occurrences (all)	0	18	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	3	0	
Micturition urgency			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 27 (51.85%)	79 / 181 (43.65%)	
occurrences (all)	21	123	
Back pain			

subjects affected / exposed	4 / 27 (14.81%)	18 / 181 (9.94%)	
occurrences (all)	4	21	
Pain in extremity			
subjects affected / exposed	2 / 27 (7.41%)	13 / 181 (7.18%)	
occurrences (all)	5	14	
Myalgia			
subjects affected / exposed	3 / 27 (11.11%)	18 / 181 (9.94%)	
occurrences (all)	4	23	
Muscle spasms			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 27 (0.00%)	14 / 181 (7.73%)	
occurrences (all)	0	15	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	3 / 27 (11.11%)	0 / 181 (0.00%)	
occurrences (all)	3	0	
Oral candidiasis			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Folliculitis			
subjects affected / exposed	3 / 27 (11.11%)	18 / 181 (9.94%)	
occurrences (all)	3	24	
Rash pustular			
subjects affected / exposed	3 / 27 (11.11%)	0 / 181 (0.00%)	
occurrences (all)	3	0	
Skin infection			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	3 / 27 (11.11%)	0 / 181 (0.00%)	
occurrences (all)	6	0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Decreased appetite			
subjects affected / exposed	10 / 27 (37.04%)	50 / 181 (27.62%)	
occurrences (all)	15	56	
Hyperglycaemia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	3	0	
Hypoalbuminaemia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	5 / 27 (18.52%)	18 / 181 (9.94%)	
occurrences (all)	7	20	
Hyponatraemia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 181 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2012	Cohort 3 was split into two – the pre-existing Cohort 3a - vemurafenib only, and a new Cohort 3b - combination therapy with vemurafenib and cetuximab. The protocol was amended to include rationale for vemurafenib and cetuximab treatment in this cohort.
18 March 2014	Additional subjects (up to 70 subjects in total) were allowed to be recruited into a study cohort if a promising response rate was demonstrated in Stage II of that cohort. The exploratory objectives for the study were revised.
16 January 2015	The secondary objectives were changed to include the evaluation of tumor assessment scans by an independent review committee (IRC) for Cohort 1 (NSCLC) and other cohorts that demonstrate clinically meaningful efficacy per investigator assessment. The presence of BRAF V600 mutations could be retrospectively confirmed. Inclusion criteria for all subjects were changed to include male or female >/=16 years of age. Inclusion criteria for solid tumors and multiple myeloma were changed so that in order for the subject to be eligible, they must be able to provide a tumor sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. IRC assessment of response rates was added a secondary efficacy endpoint focusing on Week 8, Week 16 and BOR for Cohort 1 (NSCLC) and other cohorts that demonstrate clinically meaningful efficacy per investigator assessment.
24 March 2016	Prior to the closure of the trial or should the study be closed due to Sponsor decision, it was added that the Sponsor may offer subjects who have completed the protocol-mandated minimum 12-month safety follow-up and who continue to benefit from vemurafenib therapy, the opportunity to receive continued vemurafenib via enrollment in the GO28399 extension trial. The interim analysis was changed to add efficacy analysis at 9 months for expanded cohorts. In case a cohort/indication is expanded up to 70 subjects, the primary analysis for efficacy will occur once all subjects have been followed up for 9 months after last subject had been enrolled in that cohort, or the subject develops progressive disease, withdraws consent, or is lost to follow-up, whichever occurred first.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported