Clinical trial results:
An Open-Label, 2-Cohort, Multicenter, Phase 2 Study of E7080 in Previously Treated Subjects With Unresectable Stage III or Stage IV Melanoma

Summary

EudraCT number	2010-019526-14
Trial protocol	GB DE
Global end of trial date	05 November 2014

Results information

Result version number	v1 (current)
This version publication date	30 October 2016
First version publication date	30 October 2016

Trial information

Trial identification

Sponsor protocol code	E7080-G000-206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01136967
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai
Sponsor organisation address	100 Tice Boulevard, Woodcliff Lake, United States, 07677
Public contact	Eisai Call Center, Eisai Inc., 888 422-4743, lmedinfo@eisai.net
Scientific contact	Eisai Call Center, Eisai Inc., 888 422-4743, lmedinfo@eisai.net

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	15 April 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2013
Global end of trial reached?	Yes
Global end of trial date	05 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were:
• To assess the objective response rate (ORR) (complete response + partial response [CR + PR]) of lenvatinib in subjects with unresectable Stage III or Stage IV melanoma not harboring the V600E BRAF mutation and disease progression following up to 2 prior systemic anticancer regiments for unresectable Stage III or Stage IV melanoma (Cohort 1).
• To assess the ORR of lenvatinib in subjects with unresectable Stage III or Stage IV melanoma harboring the activating BRAF mutations (mainly the V600E mutation) and disease progression following BRAF V600E-targeted therapy (Cohort 2).

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:
- Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008)
- International Conference on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal
Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP Subject Information and Informed Consent.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	26 August 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	United States: 116
Country: Number of subjects enrolled	Australia: 30

Worldwide total number of subjects	182
EEA total number of subjects	36

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)	115
From 65 to 84 years	67
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at a total of 40 sites in Australia, Germany, United Kingdom, and United States.

Pre-assignment

Screening details:

A total of 298 participants were screened. Of these, 116 were screen failures and 182 received treatment (93 participants in Cohort 1 and 89 participants in Cohort 2). Out of the 116 screen failures, 97 participants fail to meet the inclusion/exclusion criteria, 11 withdrew consent, and 8 were excluded for other reasons.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (V600E BRAF negative)

Arm description:

Cohort 1 (V600E BRAF negative) enrolled participants not harboring the V600E BRAF mutation with disease progression following up to 2 prior systemic anticancer regimens excluding anti-vascular endothelial growth factor (anti-VEGF) for unresectable Stage III or Stage IV melanoma. Participants received lenvatinib 24 mg orally, once daily continuously in 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	E7080
Other name	Lenvima
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

24 mg lenvatinib, once daily (two 10-mg capsules and one 4-mg capsule) was administered at approximately the same time in the morning without regard to food intake for 28 days from Cycle 1 onward. If a dose was missed, it was to be taken within the 12 hours following the usual time of the morning dose. If more than 12 hours had elapsed from the time of the usual daily dose, lenvatinib was to be taken the next day at the usual time in the morning. If in the event a participant vomited after study drug administration, they were not to take another dose until the next scheduled dose.

Arm title	Cohort 2 (V600E BRAF positive)

Arm description:

Cohort 2 (V600E BRAF positive) enrolled participants harboring the activating BRAF mutations (mainly the V600E mutation) with disease progression following BRAF V600E-targeted therapy. Participants received lenvatinib 24 mg orally, once daily continuously in 28-day cycles. In addition to BRAF V600E-targeted therapy, participants may have received up to 2 prior systemic anticancer regimens (including immunotherapies but excluding anti-vascular endothelial growth factor (anti-VEGF) therapies) for unresectable Stage III or Stage IV disease.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	Lenvima, E7080
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

24 mg lenvatinib, once daily (two 10-mg capsules and one 4-mg capsule) was administered at approximately the same time in the morning without regard to food intake for 28 days from Cycle 1 onward. If a dose was missed, it was to be taken within the 12 hours following the usual time of the morning dose. If more than 12 hours had elapsed from the time of the usual daily dose, lenvatinib was to be taken the next day at the usual time in the morning. If in the event a participant vomited after study drug administration, they were not to take another dose until the next scheduled dose.

Number of subjects in period 1	Cohort 1 (V600E BRAF negative)	Cohort 2 (V600E BRAF positive)
Started	93	89
Completed	69	62
Not completed	24	27
Clinical progression	3	5
Participant choice	8	3
Consent withdrawn by subject	1	2
Increase in lesion size	-	2
Radiation	1	-
Adverse event, non-fatal	9	12
Non-compliance	1	-
Diagnosis of second primary cancer	-	1
Investigator's choice	1	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 (V600E BRAF negative)
Reporting group description:	
Cohort 1 (V600E BRAF negative) enrolled participants not harboring the V600E BRAF mutation with disease progression following up to 2 prior systemic anticancer regimens excluding anti-vascular endothelial growth factor (anti-VEGF) for unresectable Stage III or Stage IV melanoma. Participants received lenvatinib 24 mg orally, once daily continuously in 28-day cycles.	
Reporting group title	Cohort 2 (V600E BRAF positive)
Reporting group description:	
Cohort 2 (V600E BRAF positive) enrolled participants harboring the activating BRAF mutations (mainly the V600E mutation) with disease progression following BRAF V600E-targeted therapy. Participants received lenvatinib 24 mg orally, once daily continuously in 28-day cycles. In addition to BRAF V600E-targeted therapy, participants may have received up to 2 prior systemic anticancer regimens (including immunotherapies but excluding anti-vascular endothelial growth factor (anti-VEGF) therapies) for unresectable Stage III or Stage IV disease.	

Reporting group values	Cohort 1 (V600E BRAF negative)	Cohort 2 (V600E BRAF positive)	Total
Number of subjects	93	89	182
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
geometric mean	62.5	55	
standard deviation	± 11.71	± 14.18	-
Gender categorical Units: Subjects			
Female	29	39	68
Male	64	50	114
AJCC Melanoma Tumor, Node, Metastasis (TNM) Stage at Study Entry Units: Subjects			
Unresectable Stage III	5	7	12
Unresectable Stage IV	88	82	170

End points

End points reporting groups

Reporting group title	Cohort 1 (V600E BRAF negative)

Reporting group description:

Cohort 1 (V600E BRAF negative) enrolled participants not harboring the V600E BRAF mutation with disease progression following up to 2 prior systemic anticancer regimens excluding anti-vascular endothelial growth factor (anti-VEGF) for unresectable Stage III or Stage IV melanoma. Participants received lenvatinib 24 mg orally, once daily continuously in 28-day cycles.

Reporting group title	Cohort 2 (V600E BRAF positive)

Reporting group description:

Cohort 2 (V600E BRAF positive) enrolled participants harboring the activating BRAF mutations (mainly the V600E mutation) with disease progression following BRAF V600E-targeted therapy. Participants received lenvatinib 24 mg orally, once daily continuously in 28-day cycles. In addition to BRAF V600E-targeted therapy, participants may have received up to 2 prior systemic anticancer regimens (including immunotherapies but excluding anti-vascular endothelial growth factor (anti-VEGF) therapies) for unresectable Stage III or Stage IV disease.

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

ORR, (ORR = CR + PR) was defined as the percentage of participants in each cohort who had a best overall response (BOR) of complete response (CR) or partial response (PR) based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 for target lesions assessed by magnetic resonance imaging/computed tomography (MRI/CT) scans and independent radiologic review (IRR). A BOR of CR required confirmation by a subsequent CR assessment at least 4 weeks later. A BOR of PR required confirmation by a subsequent assessment of CR or PR at least 4 weeks later. CR was defined as the disappearance of all target lesions. Any pathological lymph nodes (target or non-target) had to have a reduction in short axis to less than 10 millimeters. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The Full Analysis Set (Intent-to-Treat [ITT] Analysis Set) included all participants who received at least 1 dose lenvatinib.

End point type	Primary

End point timeframe:

From date of first dose of study drug until all participants completed a minimum of 6 cycles (28-day cycles) or discontinued treatment prior to end of Cycle 6 by the date of data cutoff (15 Jan 2012 and 15 Apr 2013 for Cohort 1 and Cohort 2, respectively)

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: For each cohort, the null hypothesis that ORR is ≤10% was tested against the alternative hypothesis of an ORR ≥20%, using the 1-sample exact test of a single proportion, at the 1-sided 0.05 level. ORR is shown with corresponding 2-sided, exact binomial 95% confidence interval. Statistical results are found in the table for ORR with 95% CI.

End point values	Cohort 1 (V600E BRAF negative)	Cohort 2 (V600E BRAF positive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	89		
Units: Percentage of participants				
number (confidence interval 95%)	8.6 (3.8 to 16.2)	9 (4 to 16.9)		

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 measured as the time from the date of first administration of study treatment until the date of first documentation of disease progression or date of death from any cause (whichever occurred first), as determined by IRR and Investigator based on RECIST v1.1. Disease progression per RECIST v1.1 was defined as at least a 20% relative increase and 5 mm absolute increase in the sum of diameters of target lesions (taking as reference the smallest sum on study) recorded since the treatment started or the appearance of 1 or more new lesions. PFS was analyzed using Kaplan-Meier (1958) product-limit estimates. Data were presented with 2-sided 95% CI when an adequate number of at risk participants warranted the estimates in the table below. The Full Analysis Set (ITT Analysis Set) was used and included all participants who received at least 1 dose lenvatinib.

End point type	Secondary

End point timeframe:

From date of first dose of study drug until documentation of disease progression or death from any cause (whichever occurred first) or up to data cutoff (15 Jan 2012 and 15 Apr 2013 for Cohort 1 and Cohort 2, respectively), up to approximately 2.9 years

End point values	Cohort 1 (V600E BRAF negative)	Cohort 2 (V600E BRAF positive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	89		
Units: Months				
median (confidence interval 95%)				
Determined by IRR	3.7 (2.5 to 4.2)	1.8 (1.8 to 2.2)		
Determined by Investigator	3.7 (3.6 to 4.2)	2.3 (1.9 to 3.4)		

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 the length of time in months from the date of first administration of study drug until the date of death from any cause, and was based on the data cutoff date for each cohort. OS was analyzed using Kaplan-Meier (1958) product-limit estimates. Data were presented with 2-sided 95% CI when an adequate number of at risk participants warranted the estimates in the table below. The Full Analysis Set (ITT Analysis Set) was used and included all participants who received at least 1 dose lenvatinib.

End point type	Secondary

End point timeframe:

From date of first dose of study drug until date of death from any cause or up to data cutoff (15 Jan 2012 and 15 Apr 2013 for Cohort 1 and Cohort 2, respectively), up to approximately 2.9 years

End point values	Cohort 1 (V600E BRAF negative)	Cohort 2 (V600E BRAF positive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	89		
Units: Months				
median (confidence interval 95%)	8.9 (8.3 to 99999)	6.3 (5.2 to 8.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

DCR, (DCR = CR + PR + SD) was defined as the percentage of participants who had a BOR of CR or PR or stable disease (SD). To be assigned a BOR of SD, the time from the first administration of study drug until the date of documented SD needed to be greater than or equal to seven weeks based on IRR and Investigator's assessment. The Full Analysis Set (ITT Analysis Set) was used and included all participants who received at least 1 dose lenvatinib.

End point type	Secondary

End point timeframe:

From date of first dose of study drug until documentation of disease progression or death from any cause (whichever occurred first) or up to data cutoff (15 Jan 2012 and 15 Apr 2013 for Cohort 1 and Cohort 2, respectively), up to approximately 2.9 years

End point values	Cohort 1 (V600E BRAF negative)	Cohort 2 (V600E BRAF positive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	89		
Units: Percentage of participants				
number (confidence interval 95%)				
Determined by IRR	52.7 (42.1 to 63.1)	34.8 (25 to 45.7)		
Determined by Investigator	64.5 (53.9 to 74.2)	48.3 (37.6 to 59.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

CBR, (CBR = CR + PR + durable SD rate) was defined as the percentage of participants who had a BOR of CR or PR or durable SD (SD lasting greater than or equal to 23 weeks) based on IRR and Investigator's assessment. The Full Analysis Set (ITT Analysis Set) was used and included all participants who received at least 1 dose lenvatinib.

End point type	Secondary

End point timeframe:

From date of first dose of study drug until documentation of disease progression or death from any cause (whichever occurred first) or up to data cutoff (15 Jan 2012 and 15 Apr 2013 for Cohort 1 and Cohort 2, respectively), up to approximately 2.9 years

End point values	Cohort 1 (V600E BRAF negative)	Cohort 2 (V600E BRAF positive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	89		
Units: Percentage of participants				
number (confidence interval 95%)				
Determined by IRR	31.2 (22 to 41.6)	14.6 (8 to 23.7)		
Determined by Investigator	33.3 (23.9 to 43.9)	20.2 (12.4 to 30.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs)/ Serious Adverse Events (SAEs) as a Measure of Safety and Tolerability of Lenvatinib

End point title	Number of Participants with Adverse Events (AEs)/ Serious Adverse Events (SAEs) as a Measure of Safety and Tolerability of Lenvatinib

End point description:

Safety was assessed by monitoring and recording all AEs including all Common Terminology Criteria for Adverse Events (CTCAE) grades and SAEs; regular monitoring of hematology, clinical chemistry, and urine values; physical examinations; and regular measurement of vital signs, electrocardiograms (ECGs), and multi-gated acquisition (MUGA) scans or echocardiogram. The Safety Analysis set was used and included all participants who received at least 1 dose of lenvatinib and had at least 1 postbaseline safety evaluation.

End point type	Secondary

End point timeframe:

From date of administration of first dose up to 30 days after the last dose, or up to data cutoff (15 Jan 2012 and 15 Apr 2013 for Cohort 1 and Cohort 2, respectively), up to approximately 33 months.

End point values	Cohort 1 (V600E BRAF negative)	Cohort 2 (V600E BRAF positive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	89		
Units: Participants				
number (not applicable)				
AEs	93	89		
SAEs	39	36		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Plasma Concentration of Lenvatinib

End point title	Summary of Plasma Concentration of Lenvatinib

End point description:

Blood samples for the quantification of lenvatinib in plasma were obtained and processed using a standardized protocol. The lower limit of quantification was 0.25 ng/mL. Pharmacokinetic (PK) analysis was conducted using nonlinear mixed effects modeling. Descriptive statistics were used to summarize lenvatinib plasma concentration data. The PK analysis set was used for analysis and included all participants who received at least one dose of lenvatinib and had at least one quantifiable lenvatinib concentration.

End point type	Secondary

End point timeframe:

Predose and 2 to 12 hours postdose at Cycle 1 Day 1 (C1D1), Cycle 1 Day 15 (C1D15), and Cycle 2 Day 1 (C2D1)

End point values	Cohort 1 (V600E BRAF negative)	Cohort 2 (V600E BRAF positive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	89		
Units: ng/mL				
arithmetic mean (standard deviation)				
C1D1 Pre-dose (n = 92, 85)	0 (± 0)	0 (± 0)		
C1D1 Post-dose (n = 89, 85)	229.6 (± 148.98)	287.6 (± 168.97)		
C1D15 Pre-dose (n = 79, 77)	56.8 (± 82)	71.9 (± 104.09)		
C1D15 Post-dose (n = 80, 79)	284 (± 141.71)	332.1 (± 221.98)		
C2D1 Pre-dose (n = 78, 73)	38.7 (± 32.94)	52 (± 48.73)		
C2D1 Post-dose (n = 74, 68)	244.5 (± 182.67)	270.4 (± 143.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Concentration of Clinical Biomarkers in Whole Blood

End point title	Change from Baseline in the Concentration of Clinical Biomarkers in Whole Blood

End point description:

Blood samples were drawn at specific time points. Utilizing a standard protocol, the deoxyribonucleic acid (DNA) from whole blood was extracted and analyzed for specific biomarkers of absorption, distribution, metabolism, and excretion of lenvatinib. Some of the biomarkers analyzed included; Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), FMS Like Tyrosine Kinase 3 Ligand (Flt3l) Granulocyte Colony Stimulating Factor (G-CSF), Granulocyte Macro Colony Stimulating Factor (GM-CSF), Interleukin 1 Receptor Antagonist (IL-1RA), Interferon (IFN), Macrophage Inflammatory Protein (MIP) 1 alpha, Platelet Derived Growth Factor (PDGF), Stromal Cell Derived Factor (SDF) 1 alpha, Interleukin (IL), Transforming Growth Factor (TGF), Tumor Necrosis Factor (TNF), Vascular Endothelial Growth Factor (VEGF). The Safety Analysis set was used and included all participants who received at least one dose of lenvatinib and had at least 1 postbaseline safety evaluation.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15 (C1 D15), Cycle 2 Day 1 (C2 D1), Cycle 3 Day 1 (C3 D1), Off-Treatment/Phase Visit 98 (V98)

End point values	Cohort 1 (V600E BRAF negative)	Cohort 2 (V600E BRAF positive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	89		
Units: pg/mL				
arithmetic mean (standard deviation)				
Angiopoietin 2 76 C1D15 (n = 78, 0)	-1015.69 (± 946.596)	0 (± 0)		
Angiopoietin 2 76 C2D1 (n = 79, 0)	-832.29 (± 1257.287)	0 (± 0)		
Angiopoietin 2 76 C3D1 (n = 51, 0)	-923.82 (± 969.285)	0 (± 0)		
Angiopoietin 2 76 V98 (n = 6, 0)	-947 (± 825.037)	0 (± 0)		
Angiopoietin 2 90 C1D15 (n = 0, 69)	0 (± 0)	-1225.32 (± 1950.453)		
Angiopoietin 2 90 C2D1 (n = 0, 66)	0 (± 0)	-1100.24 (± 1378.462)		
Angiopoietin 1 C1D15 (n = 80, 70)	-3033.03 (± 8808.206)	-2717.53 (± 16689.45)		
Angiopoietin 1 C2D1 (n = 80, 67)	-2802.31 (± 10202.78)	-1743.57 (± 15546.48)		
Angiopoietin 1 C3D1 (n = 52, 0)	-859.021 (± 9994.671)	0 (± 0)		
Angiopoietin 1 V98 (n = 6, 0)	8107.4 (± 17740.05)	0 (± 0)		
Angiopoietin 2 C1D15 (n = 80, 70)	-1462.55 (± 1541.807)	-2154.27 (± 3560.003)		
Angiopoietin 2 C2D1 (n = 80, 67)	-1225.46 (± 1872.584)	-1884.44 (± 2357.198)		
Angiopoietin 2 C3D1 (n = 52, 0)	-1255.49 (± 1738.089)	0 (± 0)		
Angiopoietin 2 V98 (n = 6, 0)	-1374.18 (± 1158.29)	0 (± 0)		

CD40 Ligand C1D15 (n = 59, 70)	-24020.8 (± 62788.25)	-4678.66 (± 41191.73)		
CD40 Ligand C2D1 (n = 58, 67)	-22957.6 (± 73677.44)	-7254.75 (± 37794.55)		
CD40 Ligand C3D1 (n = 35, 0)	-16700.9 (± 48016.07)	0 (± 0)		
CD40 Ligand V98 (n = 3, 0)	2192.177 (± 86909.97)	0 (± 0)		
EGF 2 C1D15 (n = 74, 62)	-46.493 (± 101.0772)	-0.516 (± 219.9787)		
EGF 2 C2D1 (n = 76, 58)	-39.636 (± 125.0664)	-29.803 (± 121.1705)		
EGF 2 C3D1 (n = 47, 0)	-37.6 (± 113.8543)	0 (± 0)		
EGF 2 V98 (n = 6, 0)	-2.23 (± 191.4129)	0 (± 0)		
EGF 59 C1D15 (n = 77, 0)	-37.07 (± 81.051)	0 (± 0)		
EGF 59 C2D1 (n = 78, 0)	-31.58 (± 96.2)	0 (± 0)		
EGF 59 C3D1 (n = 50, 0)	-24.49 (± 93.102)	0 (± 0)		
EGF 59 V98 (n = 6, 0)	10.17 (± 137.755)	0 (± 0)		
EGF 80 C1D15 (n = 0, 65)	0 (± 0)	-31.519 (± 126.2579)		
EGF 80 C2D1 (n = 0, 65)	0 (± 0)	-32.171 (± 121.7805)		
Eotaxin-4 C1D15 (n = 78, 70)	51.456 (± 117.1266)	46.538 (± 128.398)		
Eotaxin-4 C2D1 (n = 79, 67)	99.974 (± 207.0243)	60.919 (± 114.6134)		
Eotaxin-4 C3D1 (n = 50, 0)	89.878 (± 108.6392)	0 (± 0)		
Eotaxin-4 V98 (n = 6, 0)	104.613 (± 157.7527)	0 (± 0)		
FGF 2 C1D15 (n = 77, 57)	-4.294 (± 51.3985)	8.325 (± 136.3433)		
FGF 2 C2D1 (n = 78, 54)	-8.085 (± 48.8273)	-8.003 (± 144.9054)		
FGF 2 C3D1 (n = 51, 0)	7.443 (± 45.731)	0 (± 0)		
FGF 2 V98 (n = 6, 0)	-3.917 (± 62.3623)	0 (± 0)		
FGF 23 C1D15 (n = 32, 0)	6.549 (± 22.5297)	0 (± 0)		
FGF 23 C2D1 (n = 36, 0)	6.496 (± 27.2305)	0 (± 0)		
FGF 23 C3D1 (n = 22, 0)	6.691 (± 24.5203)	0 (± 0)		
FGF 23 V98 (n = 2, 0)	13.43 (± 36.713)	0 (± 0)		
FGF 4 C1D15 (n = 68, 25)	-24.226 (± 100.6823)	50.369 (± 253.9626)		
FGF 4 C2D1 (n = 68, 23)	-15.491 (± 104.9991)	55.785 (± 264.4585)		
FGF 4 C3D1 (n = 47, 0)	5.283 (± 130.3452)	0 (± 0)		
FGF 4 V98 (n = 5, 0)	33.86 (± 185.4616)	0 (± 0)		
FGF Basic Form C1D15 (n = 68, 44)	-0.597 (± 18.6851)	43.457 (± 224.9856)		

FGF Basic Form C2D1 (n = 68, 41)	-1.212 (± 38.4131)	64.237 (± 328.6676)		
FGF Basic Form C3D1 (n = 44, 0)	2.06 (± 29.2405)	0 (± 0)		
FGF Basic Form V98 (n = 5, 0)	18.384 (± 28.6214)	0 (± 0)		
Flt3l C1D15 (n = 78, 69)	-0.037 (± 32.5371)	-8.877 (± 23.0368)		
Flt3l C2D1 (n = 79, 66)	5.135 (± 28.0359)	-1.362 (± 39.2251)		
Flt3l C3D1 (n = 51, 0)	5.439 (± 24.1985)	0 (± 0)		
Flt3l V98 (n = 6, 0)	13.367 (± 17.7279)	0 (± 0)		
Fractalkine C1D15 (n = 68, 56)	-11.7 (± 94.5115)	38.67 (± 237.5045)		
Fractalkine C2D1 (n = 69, 54)	-1.175 (± 70.0858)	4.663 (± 58.195)		
Fractalkine C3D1 (n = 47, 0)	-5.588 (± 116.3955)	0 (± 0)		
Fractalkine V98 (n = 4, 0)	15.838 (± 90.6004)	0 (± 0)		
G-CSF C1D15 (n = 78, 70)	4.329 (± 20.8343)	6.368 (± 61.7181)		
G-CSF C2D1 (n = 79, 66)	7.366 (± 32.5552)	12.601 (± 72.5113)		
G-CSF C3D1 (n = 50, 0)	11.292 (± 24.1828)	0 (± 0)		
G-CSF V98 (n = 6, 0)	34.653 (± 101.7055)	0 (± 0)		
GM-CSF C1D15 (n = 36, 26)	0.767 (± 16.9314)	44.665 (± 220.9124)		
GM-CSF C2D1 (n = 42, 27)	4.371 (± 38.3355)	139.491 (± 725.0903)		
GM-CSF C3D1 (n = 29, 0)	10.036 (± 49.8538)	0 (± 0)		
GM-CSF V98 (n = 2, 0)	-1.495 (± 5.1831)	0 (± 0)		
Growth Regulated Oncogene C1D15 (n = 0, 70)	0 (± 0)	-141.838 (± 410.3579)		
Growth Regulated Oncogene C2D1 (n = 0, 67)	0 (± 0)	-120.148 (± 456.3073)		
Hepatocyte Growth Factor C1D15 (n = 78, 68)	102.527 (± 1309.407)	-91.79 (± 781.2225)		
Hepatocyte Growth Factor C2D1 (n = 78, 65)	-126.667 (± 693.2257)	-147.796 (± 411.1836)		
Hepatocyte Growth Factor C3D1 (n = 51, 0)	61.257 (± 1062.326)	0 (± 0)		
Hepatocyte Growth Factor V98 (n = 6, 0)	404.7 (± 456.813)	0 (± 0)		
Interferon Gamma C1D15 (n = 31, 18)	4.072 (± 19.3994)	33.743 (± 100.3678)		
Interferon Gamma C2D1 (n = 32, 18)	-0.392 (± 14.8083)	-10.164 (± 170.9869)		
Interferon Gamma C3D1 (n = 21, 0)	2.986 (± 5.7591)	0 (± 0)		
Interferon Gamma V98 (n = 2, 0)	2.455 (± 5.2255)	0 (± 0)		
Interleukin 1 alpha C1D15 (n = 25, 16)	0.159 (± 7.9441)	67.203 (± 200.9806)		
Interleukin 1 alpha C2D1 (n = 28, 16)	0.226 (± 8.2728)	-36.352 (± 198.1416)		

Interleukin 1 alpha C3D1 (n = 22, 0)	-0.14 (± 13.7136)	0 (± 0)		
Interleukin 1 alpha V98 (n = 0, 0)	0 (± 0)	0 (± 0)		
Interleukin 1 Beta C1D15 (n = 16, 6)	0.279 (± 1.9668)	59.768 (± 137.6657)		
Interleukin 1 Beta C2D1 (n = 19, 6)	1.198 (± 5.0044)	27.69 (± 61.2456)		
Interleukin 1 Beta C3D1 (n = 13, 0)	1.882 (± 11.1737)	0 (± 0)		
Interleukin 1 Beta V98 (n = 0, 0)	0 (± 0)	0 (± 0)		
IL-1RA C1D15 (n = 40, 18)	14.49 (± 63.5869)	46.381 (± 132.3985)		
IL-1RA C2D1 (n = 43, 16)	20.295 (± 61.9799)	38.131 (± 142.7521)		
IL-1RA C3D1 (n = 29, 0)	7.048 (± 30.9383)	0 (± 0)		
IL-1RA V98 (N = 5, 0)	84.614 (± 178.159)	0 (± 0)		
Interleukin 12 (p40) C1D15 (n = 45, 19)	14.514 (± 73.9806)	5.458 (± 28.8514)		
Interleukin 12 (p40) C2D1 (n = 49, 19)	16.052 (± 40.3849)	918.03 (± 3917.868)		
Interleukin 12 (p40) C3D1 (n = 35, 0)	11.183 (± 36.3506)	0 (± 0)		
Interleukin 12 (p40) V98 (n = 2, 0)	-8.13 (± 5.7276)	0 (± 0)		
Interleukin 12 (p70) C1D15 (n = 17, 14)	1.241 (± 18.8429)	27.919 (± 62.8944)		
Interleukin 12 (p70) C2D1 (n = 21, 14)	-5.622 (± 28.6381)	7.82 (± 71.1505)		
Interleukin 12 (p70) C3D1 (n = 15, 0)	-6.099 (± 19.5015)	0 (± 0)		
Interleukin 12 (p70) V98 (n = 2, 0)	11.275 (± 20.0182)	0 (± 0)		
Interleukin 10 C1D15 (n = 34, 40)	-5.17 (± 38.0092)	-7.611 (± 22.1926)		
Interleukin 10 C2D1 (n = 37, 41)	-1.901 (± 33.6203)	1.687 (± 72.7629)		
Interleukin 10 C3D1 (n = 22, 0)	4.136 (± 10.8185)	0 (± 0)		
Interleukin 10 V98 (n = 2, 0)	-28.065 (± 41.7547)	0 (± 0)		
Interleukin 13 C1D15 (n = 22, 5)	0.961 (± 5.0066)	8.574 (± 13.4754)		
Interleukin 13 C2D1 (n = 23, 5)	2.451 (± 7.6374)	8.536 (± 18.522)		
Interleukin 13 C3D1 (n = 17, 0)	5.404 (± 16.4719)	0 (± 0)		
Interleukin 13 V98 (n = 0, 0)	0 (± 0)	0 (± 0)		
Interleukin 15 C1D15 (n = 21, 8)	0.128 (± 2.2957)	85.619 (± 234.7106)		
Interleukin 15 C2D1 (n = 23, 9)	1.403 (± 4.163)	574.776 (± 1709.927)		
Interleukin 15 C3D1 (n = 16, 0)	-0.178 (± 3.6993)	0 (± 0)		
Interleukin 15 V98 (n = 1, 0)	3.93 (± 3.93)	0 (± 0)		
Interleukin 17 C1D15 (n = 24, 9)	3.434 (± 8.6463)	4.567 (± 12.1008)		
Interleukin 17 C2D1 (n = 24, 11)	1.264 (± 8.0963)	3.035 (± 15.8736)		
Interleukin 17 C3D1 (n = 15, 0)	0.011 (± 3.41)	0 (± 0)		

Interleukin 17 V98 (n = 2, 0)	8.44 (± 11.7663)	0 (± 0)		
Interleukin 2 C1D15 (n = 14, 6)	-1.004 (± 7.1024)	173.878 (± 397.2754)		
Interleukin 2 C2D1 (n = 9, 6)	5.853 (± 20.3294)	191.41 (± 461.1991)		
Interleukin 2 C3D1 (n = 11, 0)	2.647 (± 19.5979)	0 (± 0)		
Interleukin 2 V98 (n = 0, 0)	0 (± 0)	0 (± 0)		
Interleukin 4 C1D15 (n = 23, 39)	8.169 (± 30.0305)	12.815 (± 77.431)		
Interleukin 4 C2D1 (n = 23, 40)	20.167 (± 77.0619)	7.815 (± 54.5735)		
Interleukin 4 C3D1 (n = 20, 0)	6.583 (± 20.3824)	0 (± 0)		
Interleukin 4 V98 (n = 0, 0)	0 (± 0)	0 (± 0)		
Interleukin 5 C1D15 (n = 9, 5)	0.311 (± 1.1314)	6.088 (± 7.5239)		
Interleukin 5 C2D1 (n = 10, 6)	0.205 (± 1.5931)	11.382 (± 9.8663)		
Interleukin 5 C3D1 (n = 6, 0)	-0.327 (± 1.1102)	0 (± 0)		
Interleukin 6 C1D15 (n = 35, 39)	0.166 (± 6.8774)	3.784 (± 30.0715)		
Interleukin 6 C2D1 (n = 34, 36)	4.778 (± 34.0254)	5.524 (± 32.1205)		
Interleukin 6 C3D1 (n = 21, 0)	2.027 (± 7.3121)	0 (± 0)		
Interleukin 6 V98 (n = 4, 0)	3.16 (± 6.6276)	0 (± 0)		
Interleukin 7 C1D15 (n = 26, 20)	1.267 (± 7.3732)	2.167 (± 8.8122)		
Interleukin 7 C2D1 (n = 28, 21)	2.413 (± 8.8367)	5.744 (± 18.4339)		
Interleukin 7 C3D1 (n = 19, 0)	0.616 (± 5.059)	0 (± 0)		
Interleukin 7 V98 (n = 2, 0)	20.76 (± 28.0439)	0 (± 0)		
Interleukin 8 C1D15 (n = 78, 68)	-5.801 (± 46.1572)	-20.769 (± 52.1135)		
Interleukin 8 C2D1 (n = 79, 65)	-5.431 (± 43.4197)	-14.303 (± 57.9561)		
Interleukin 8 C3D1 (n = 50, 0)	-7.348 (± 43.0509)	0 (± 0)		
Interleukin 8 V98 (n = 6, 0)	26.982 (± 32.7795)	0 (± 0)		
IFN gamma Induced Protein 10 C1D15 (n = 78, 70)	453.684 (± 1446.583)	184.891 (± 501.5782)		
IFN gamma Induced Protein 10 C2D1 (n = 79, 67)	246.194 (± 337.6926)	306.075 (± 792.5621)		
IFN gamma Induced Protein 10 C3D1 (n = 50, 0)	201.923 (± 483.5088)	0 (± 0)		
IFN gamma Induced Protein 10 V98 (n = 6, 0)	359.872 (± 501.1082)	0 (± 0)		
Monocyte Chemotactic Protein 1 C1D15 (n = 78, 70)	0.733 (± 423.2721)	-101.58 (± 371.5381)		
Monocyte Chemotactic Protein 1 C2D1 (n = 79, 67)	-19.036 (± 372.5242)	128.749 (± 541.1034)		
Monocyte Chemotactic Protein 1 C3D1 (n = 50, 0)	13.542 (± 370.37)	0 (± 0)		
Monocyte Chemotactic Protein 1 V98 (n = 6, 0)	-128.627 (± 1234.589)	0 (± 0)		

MIP 1 alpha C1D15 (n = 76, 51)	-1.842 (± 11.9129)	-0.32 (± 38.5273)		
MIP 1 alpha C2D1 (n = 76, 46)	-2.098 (± 12.0121)	-0.473 (± 35.4447)		
MIP 1 alpha C3D1 (n = 49, 0)	-1.167 (± 15.9038)	0 (± 0)		
MIP 1 alpha V98 (n = 6, 0)	7.563 (± 7.8802)	0 (± 0)		
MIP 1 beta C1D15 (n = 78, 70)	0.032 (± 20.149)	5.746 (± 64.1386)		
MIP 1 beta C2D1 (n = 79, 67)	-1.198 (± 31.1522)	31.277 (± 261.346)		
MIP 1 beta C3D1 (n = 50, 0)	1.85 (± 15.208)	0 (± 0)		
MIP 1 beta V98 (n = 6, 0)	7.518 (± 11.9566)	0 (± 0)		
PDGF AA 31 P1 C1D15 (n = 0, 69)	0 (± 0)	-183.36 (± 2260.11)		
PDGF AA 31 P1 C2D1 (n = 0, 66)	0 (± 0)	-268.83 (± 2054.666)		
PDGF AB C1D15 (n = 76, 69)	-36.637 (± 353.6898)	-121.278 (± 325.1308)		
PDGF AB C2D1 (n = 77, 66)	-99.852 (± 338.5816)	-80.778 (± 363.1249)		
PDGF AB C3D1 (n = 50, 0)	-7.702 (± 311.6834)	0 (± 0)		
PDGF AB V98 (n = 5, 0)	130.8 (± 382.6282)	0 (± 0)		
PDGF BB C1D15 (n = 78, 69)	-120.317 (± 1758.765)	-567.664 (± 1385.674)		
PDGF BB C2D1 (n = 79, 66)	-435.311 (± 1961.744)	-371.888 (± 1186.644)		
PDGF BB C3D1 (n =51, 0)	333.637 (± 1516.15)	0 (± 0)		
PDGF BB V98 (n = 6, 0)	174.083 (± 3221.901)	0 (± 0)		
Placental Derived Growth Factor C1D15 (n = 78, 56)	55.444 (± 55.0671)	26.465 (± 29.8457)		
Placental Derived Growth Factor C2D1 (n = 79, 54)	50.439 (± 58.2571)	51.359 (± 76.639)		
Placental Derived Growth Factor C3D1 (n = 51, 0)	61.08 (± 58.2969)	0 (± 0)		
Placental Derived Growth Factor V98 (n = 6, 0)	112.683 (± 110.3416)	0 (± 0)		
Chemokine Ligand 5 C1D15 (n = 0, 70)	0 (± 0)	-2373.94 (± 46225.7)		
Chemokine Ligand 5 C1D15 C2D1 (n = 0, 67)	0 (± 0)	551.64 (± 49492.45)		
SDF 1 alpha C1D15 (n = 77, 69)	441.305 (± 385.8988)	506.768 (± 487.7603)		
SDF 1 alpha C2D1 (n = 77, 66)	520.051 (± 510.8558)	647.435 (± 470.0962)		
SDF 1 alpha C3D1 (n = 51, 0)	509.483 (± 550.4383)	0 (± 0)		
SDF 1 alpha V98 (n = 5, 0)	836.532 (± 686.4434)	0 (± 0)		
Soluble IL2 Receptor alpha C1D15 (n = 65, 67)	-25.869 (± 86.0991)	-414.669 (± 765.1544)		
Soluble IL2 Receptor alpha C2D1 (n = 67, 64)	-13.695 (± 65.5643)	-290.918 (± 1023.339)		
Soluble IL2 Receptor alpha C3D1 (n = 41, 0)	-12.233 (± 31.5415)	0 (± 0)		

Soluble IL2 Receptor alpha V98 (n = 4, 0)	-19.238 (± 43.0942)	0 (± 0)		
TGF alpha C1D15 (n = 52, 48)	-0.874 (± 4.6605)	21.148 (± 168.7766)		
TGF alpha C2D1 (n = 51, 43)	-0.35 (± 6.5375)	-6.019 (± 24.3258)		
TGF alpha C3D1 (n = 31, 0)	1.165 (± 11.8825)	0 (± 0)		
TGF alpha V98 (n = 3, 0)	2.59 (± 3.4672)	0 (± 0)		
Tie-2 C1D15 (n = 77, 69)	-2971.95 (± 2397.523)	-3573.86 (± 2996.714)		
Tie-2 C2D1 (n = 78, 66)	-3447.69 (± 3577.179)	-4088.21 (± 3191.981)		
Tie-2 C3D1 (n = 51, 0)	-2811.77 (± 3459.193)	0 (± 0)		
Tie-2 V98 (n = 5, 0)	-1924 (± 3215.568)	0 (± 0)		
TNF alpha C1D15 (n = 77, 67)	-0.233 (± 4.9747)	1.451 (± 24.8216)		
TNF alpha C2D1 (n = 78, 64)	0.039 (± 3.954)	1.741 (± 15.0677)		
TNF alpha C3D1 (n = 49, 0)	0.614 (± 4.6336)	0 (± 0)		
TNF alpha V98 (n = 6, 0)	3.027 (± 4.7343)	0 (± 0)		
VEGF C1D15 (n = 78, 66)	-13.294 (± 112.6871)	10.709 (± 285.2533)		
VEGF C2D1 (n = 78, 62)	-11.523 (± 122.6064)	-26.215 (± 239.496)		
VEGF C3D1 (n = 50, 0)	16.732 (± 160.3096)	0 (± 0)		
VEGF V98 (n = 6, 0)	155.638 (± 352.8309)	0 (± 0)		
VEGF A C1D15 (n = 78, 69)	78.868 (± 174.8011)	92.748 (± 273.619)		
VEGF A C2D1 (n = 79, 66)	76.041 (± 194.1394)	140.664 (± 336.9135)		
VEGF A C3D1 (n = 51, 0)	116.8 (± 233.1657)	0 (± 0)		
VEGF A V98 (n = 6, 0)	465.833 (± 515.7676)	0 (± 0)		
VEGF D C1D15 (n = 78, 21)	0.953 (± 87.6513)	3.404 (± 42.7585)		
VEGF D C2D1 (n = 78, 19)	-9.776 (± 98.0905)	11.043 (± 116.5445)		
VEGF D C3D1 (n = 51, 0)	9.894 (± 57.114)	0 (± 0)		
VEGF D V98 (n = 6, 0)	-21.317 (± 88.6689)	0 (± 0)		
VEGF Rec 1 C1D15 (n = 78, 55)	593.613 (± 3109.334)	-221.867 (± 799.9202)		
VEGF Rec 1 C2D1 (n = 79, 53)	-3.971 (± 739.7875)	-243.661 (± 1031.237)		
VEGF Rec 1 C3D1 (n = 51, 0)	-209.863 (± 809.7744)	0 (± 0)		
VEGF Rec 1 V98 (n = 6, 0)	-15.567 (± 90.6274)	0 (± 0)		
VEGF Rec 2 C1D15 (n = 78, 67)	-10110.1 (± 5626.013)	-8842.04 (± 6078.715)		
VEGF Rec 2 C2D1 (n = 78, 64)	-9369.17 (± 17982.06)	-10676.6 (± 7064.083)		

VEGF Rec 2 C3D1 (n = 51, 0)	-11389.6 (± 10955.16)	0 (± 0)		
VEGF Rec 2 V98 (n = 6, 0)	-9021.22 (± 5921.962)	0 (± 0)		
VEGF Rec 3 C1D15 (n = 70, 61)	-1174.65 (± 2226.789)	-2251.87 (± 3231.149)		
VEGF Rec 3 C2D1 (n = 68, 58)	-1320.73 (± 3138.381)	-2523.26 (± 3550.729)		
VEGF Rec 3 C3D1 (n = 47, 0)	-1488.14 (± 3687.877)	0 (± 0)		
VEGF Rec 3 V98 (n = 5, 0)	-1201.68 (± 2441.574)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of administration of first dose up to 30 days after the last dose, or up to data cutoff (15 Jan 2012 and 15 Apr 2013 for Cohort 1 and Cohort 2, respectively), up to approximately 33 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Cohort 1 (V600E BRAF Negative)

Reporting group description:

Cohort 1 (V600E BRAF negative) enrolled participants not harboring the V600E BRAF mutation with disease progression following up to 2 prior systemic anticancer regimens (excluding anti-VEGF) for unresectable Stage III or Stage IV melanoma. Participants received lenvatinib 24 mg orally, once daily continuously in 28-day cycles.

Reporting group title	Cohort 2 (V600E BRAF Positive)

Reporting group description:

Cohort 2 (V600E BRAF positive) enrolled participants harboring the activating BRAF mutations (mainly the V600E mutation) with disease progression following BRAF V600E-targeted therapy. Participants received lenvatinib 24 mg orally, once daily continuously in 28-day cycles.

Serious adverse events	Cohort 1 (V600E BRAF Negative)	Cohort 2 (V600E BRAF Positive)	
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 93 (41.94%)	36 / 89 (40.45%)	
number of deaths (all causes)	42	64	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			

subjects affected / exposed	1 / 93 (1.08%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 93 (5.38%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 93 (3.23%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 93 (1.08%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 93 (0.00%)	2 / 89 (2.25%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 93 (0.00%)	2 / 89 (2.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Impaired healing			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
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 embolism			
subjects affected / exposed	3 / 93 (3.23%)	2 / 89 (2.25%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Mental status changes			
subjects affected / exposed	2 / 93 (2.15%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Chemical peritonitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial thrombosis			

subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 93 (2.15%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			

subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (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 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve palsies multiple			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
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			
Anaemia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	3 / 93 (3.23%)	3 / 89 (3.37%)	
occurrences causally related to treatment / all	2 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 93 (2.15%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 93 (2.15%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 93 (1.08%)	3 / 89 (3.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
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 / 93 (0.00%)	1 / 89 (1.12%)	
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	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder perforation			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (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	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral obstruction			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 93 (0.00%)	2 / 89 (2.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
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	2 / 93 (2.15%)	2 / 89 (2.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Appendicitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site infection			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 93 (1.08%)	0 / 89 (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 / 93 (1.08%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	2 / 93 (2.15%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 93 (1.08%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			

subjects affected / exposed	0 / 93 (0.00%)	1 / 89 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1 (V600E BRAF Negative)	Cohort 2 (V600E BRAF Positive)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 93 (100.00%)	88 / 89 (98.88%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	5 / 93 (5.38%)	1 / 89 (1.12%)	
occurrences (all)	5	1	
Hypotension			
subjects affected / exposed	4 / 93 (4.30%)	6 / 89 (6.74%)	
occurrences (all)	4	7	
Hypertension			
subjects affected / exposed	53 / 93 (56.99%)	48 / 89 (53.93%)	
occurrences (all)	111	88	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 93 (6.45%)	5 / 89 (5.62%)	
occurrences (all)	7	12	
Chills			
subjects affected / exposed	6 / 93 (6.45%)	4 / 89 (4.49%)	
occurrences (all)	6	4	
Fatigue			
subjects affected / exposed	62 / 93 (66.67%)	41 / 89 (46.07%)	
occurrences (all)	109	66	
Oedema peripheral			
subjects affected / exposed	14 / 93 (15.05%)	10 / 89 (11.24%)	
occurrences (all)	17	11	
Pain			
subjects affected / exposed	6 / 93 (6.45%)	5 / 89 (5.62%)	
occurrences (all)	7	5	

Pyrexia			
subjects affected / exposed	7 / 93 (7.53%)	10 / 89 (11.24%)	
occurrences (all)	10	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	18 / 93 (19.35%)	11 / 89 (12.36%)	
occurrences (all)	19	11	
Dysphonia			
subjects affected / exposed	26 / 93 (27.96%)	33 / 89 (37.08%)	
occurrences (all)	32	35	
Dyspnoea			
subjects affected / exposed	14 / 93 (15.05%)	13 / 89 (14.61%)	
occurrences (all)	16	13	
Epistaxis			
subjects affected / exposed	8 / 93 (8.60%)	8 / 89 (8.99%)	
occurrences (all)	9	8	
Oropharyngeal pain			
subjects affected / exposed	13 / 93 (13.98%)	5 / 89 (5.62%)	
occurrences (all)	13	5	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 93 (2.15%)	5 / 89 (5.62%)	
occurrences (all)	2	7	
Depression			
subjects affected / exposed	4 / 93 (4.30%)	5 / 89 (5.62%)	
occurrences (all)	4	8	
Insomnia			
subjects affected / exposed	7 / 93 (7.53%)	8 / 89 (8.99%)	
occurrences (all)	8	8	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 93 (3.23%)	5 / 89 (5.62%)	
occurrences (all)	3	6	
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 93 (7.53%)	3 / 89 (3.37%)	
occurrences (all)	10	4	

Blood thyroid stimulating hormone increased			
subjects affected / exposed	14 / 93 (15.05%)	7 / 89 (7.87%)	
occurrences (all)	20	7	
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 93 (5.38%)	1 / 89 (1.12%)	
occurrences (all)	7	1	
Lipase increased			
subjects affected / exposed	7 / 93 (7.53%)	3 / 89 (3.37%)	
occurrences (all)	19	3	
Weight decreased			
subjects affected / exposed	22 / 93 (23.66%)	12 / 89 (13.48%)	
occurrences (all)	24	14	
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 93 (10.75%)	16 / 89 (17.98%)	
occurrences (all)	12	19	
Dysgeusia			
subjects affected / exposed	12 / 93 (12.90%)	16 / 89 (17.98%)	
occurrences (all)	15	18	
Headache			
subjects affected / exposed	29 / 93 (31.18%)	21 / 89 (23.60%)	
occurrences (all)	37	25	
Lethargy			
subjects affected / exposed	1 / 93 (1.08%)	5 / 89 (5.62%)	
occurrences (all)	1	7	
Peripheral sensory neuropathy			
subjects affected / exposed	10 / 93 (10.75%)	2 / 89 (2.25%)	
occurrences (all)	11	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 93 (5.38%)	6 / 89 (6.74%)	
occurrences (all)	8	13	
Thrombocytopenia			
subjects affected / exposed	8 / 93 (8.60%)	9 / 89 (10.11%)	
occurrences (all)	9	15	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	21 / 93 (22.58%)	19 / 89 (21.35%)	
occurrences (all)	27	23	
Abdominal pain upper			
subjects affected / exposed	11 / 93 (11.83%)	6 / 89 (6.74%)	
occurrences (all)	13	7	
Constipation			
subjects affected / exposed	25 / 93 (26.88%)	28 / 89 (31.46%)	
occurrences (all)	30	34	
Diarrhoea			
subjects affected / exposed	44 / 93 (47.31%)	26 / 89 (29.21%)	
occurrences (all)	89	52	
Dry mouth			
subjects affected / exposed	14 / 93 (15.05%)	10 / 89 (11.24%)	
occurrences (all)	14	10	
Dyspepsia			
subjects affected / exposed	5 / 93 (5.38%)	9 / 89 (10.11%)	
occurrences (all)	6	15	
Flatulence			
subjects affected / exposed	12 / 93 (12.90%)	2 / 89 (2.25%)	
occurrences (all)	16	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	10 / 93 (10.75%)	6 / 89 (6.74%)	
occurrences (all)	10	8	
Glossodynia			
subjects affected / exposed	6 / 93 (6.45%)	2 / 89 (2.25%)	
occurrences (all)	6	2	
Nausea			
subjects affected / exposed	48 / 93 (51.61%)	36 / 89 (40.45%)	
occurrences (all)	64	45	
Oral pain			
subjects affected / exposed	10 / 93 (10.75%)	5 / 89 (5.62%)	
occurrences (all)	14	5	
Stomatitis			
subjects affected / exposed	16 / 93 (17.20%)	12 / 89 (13.48%)	
occurrences (all)	27	21	

Vomiting			
subjects affected / exposed	36 / 93 (38.71%)	32 / 89 (35.96%)	
occurrences (all)	56	49	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	16 / 93 (17.20%)	7 / 89 (7.87%)	
occurrences (all)	17	7	
Pruritus			
subjects affected / exposed	7 / 93 (7.53%)	5 / 89 (5.62%)	
occurrences (all)	8	6	
Rash			
subjects affected / exposed	16 / 93 (17.20%)	5 / 89 (5.62%)	
occurrences (all)	18	6	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	5 / 93 (5.38%)	3 / 89 (3.37%)	
occurrences (all)	5	5	
Proteinuria			
subjects affected / exposed	23 / 93 (24.73%)	17 / 89 (19.10%)	
occurrences (all)	48	34	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	17 / 93 (18.28%)	24 / 89 (26.97%)	
occurrences (all)	20	32	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	29 / 93 (31.18%)	20 / 89 (22.47%)	
occurrences (all)	37	32	
Back pain			
subjects affected / exposed	17 / 93 (18.28%)	12 / 89 (13.48%)	
occurrences (all)	19	15	
Muscle spasms			
subjects affected / exposed	7 / 93 (7.53%)	5 / 89 (5.62%)	
occurrences (all)	8	5	
Muscular weakness			

subjects affected / exposed	8 / 93 (8.60%)	3 / 89 (3.37%)	
occurrences (all)	11	4	
Musculoskeletal chest pain			
subjects affected / exposed	3 / 93 (3.23%)	6 / 89 (6.74%)	
occurrences (all)	7	8	
Musculoskeletal pain			
subjects affected / exposed	6 / 93 (6.45%)	6 / 89 (6.74%)	
occurrences (all)	8	9	
Musculoskeletal stiffness			
subjects affected / exposed	7 / 93 (7.53%)	4 / 89 (4.49%)	
occurrences (all)	10	8	
Myalgia			
subjects affected / exposed	13 / 93 (13.98%)	9 / 89 (10.11%)	
occurrences (all)	16	12	
Pain in extremity			
subjects affected / exposed	16 / 93 (17.20%)	9 / 89 (10.11%)	
occurrences (all)	18	12	
Infections and infestations			
Oral herpes			
subjects affected / exposed	5 / 93 (5.38%)	0 / 89 (0.00%)	
occurrences (all)	5	0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 93 (5.38%)	4 / 89 (4.49%)	
occurrences (all)	5	4	
Urinary tract infection			
subjects affected / exposed	10 / 93 (10.75%)	9 / 89 (10.11%)	
occurrences (all)	13	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	40 / 93 (43.01%)	30 / 89 (33.71%)	
occurrences (all)	51	41	
Dehydration			
subjects affected / exposed	6 / 93 (6.45%)	12 / 89 (13.48%)	
occurrences (all)	6	12	
Hypokalaemia			

subjects affected / exposed	6 / 93 (6.45%)	2 / 89 (2.25%)	
occurrences (all)	7	2	
Hyponatraemia			
subjects affected / exposed	8 / 93 (8.60%)	4 / 89 (4.49%)	
occurrences (all)	8	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2011	1) clarified each cohort population, allowed up to 2 prior regimens for Cohort 1 and any activating BRAF mutation (mainly V600E) for Cohort 2 2) changed study design to Simon's Optimal 2-Stage Design, which would have allowed for early termination of study if response was not sufficient 3) provided lesion size specifications for single lesion only 4) added criterion allowing subjects with brain metastases under specified circumstances 5) renal function requirement updated from 30 mL/min to 40 mL/min 6) clarified interruption/dose reduction for anemia, lymphocytopenia, and neutropenia. Reasons for changes: Clarified study population for each cohort regarding BRAF activating mutations and allowed number of prior anticancer therapies. Relaxing allowed number of prior treatments reflected a more contemporaneous approach regarding prior treatments a subject was exposed to for Stage III or IV unresectable melanoma. Also, amended entry criterion allowed for an improved enrollment rate without any detriment on the ability to assess the effect of lenvatinib on the 2 distinct study populations. Simon's Optimal 2-Stage Design was introduced to address questions/criticism from multiple sites and/or scientific committees/IRBs of not having means to control the study population exposure to lenvatinib in the event it was shown not to be efficacious in the study population. Entry criteria changed to allow subjects with brain metastasis under specific circumstances per the current understanding that a select population of subjects with brain metastasis (resected, asymptomatic disease and free of new metastasis) are good candidates for clinical trials and may equally benefit from participation in experimental clinical studies. Renal function requirement updated to reflect current understanding of lenvatinib potential for nephrotoxicity. Dose modification guidelines assessed more conservatively hematologic toxicities (anemia, neutropenia, lymphocytopenia) related to lenvatinib.
16 March 2012	Amendment 02: (1)Added exception to exclusion of timing of prior chemotherapy within 21 days, within 14 days allowed in subjects with rapid progression while receiving BRAF-targeted therapy. Reason for the change is as follows: The added language pertains to the Cohort 2 population, i.e., subjects who have a BRAF mutation and who failed a BRAF-targeted therapy. For these subjects there are no other effective treatment options and their disease is rapidly progressing once they fail the BRAF-targeted therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported