Clinical trial results:
Phase II trial of dasatinib in subjects with advanced cancers harboring DDR2 mutation or inactivating B-RAF mutation

Summary

EudraCT number	2011-003128-11
Trial protocol	DE PL GB
Global end of trial date	23 July 2014

Results information

Result version number	v1 (current)
This version publication date	22 April 2016
First version publication date	22 April 2016

Trial information

Trial identification

Sponsor protocol code	CA180-385

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01514864
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, clinical.trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, clinical.trials@bms.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	23 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 July 2014
Global end of trial reached?	Yes
Global end of trial date	23 July 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the clinical activity of dasatinib, defined as objective response rate, in subjects with cancer harboring discoidin domain receptor 2 (DDR2) mutation or inactivating B-RAF mutation.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2012
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	Poland: 1
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	19
EEA total number of subjects	12

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)	7
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 10 sites (out of 13 sites which participated in the study).

Pre-assignment

Screening details:

A total of 19 subjects were enrolled, and 14 received treatment.

Period 1

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

Blinding implementation details:

The study was open label, hence blinding was not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dasatinib, 140 mg (NSCLC With Inactivating B-RAF Mutation)

Arm description:

Subjects with non-small cell lung cancer (NSCLC) with inactivating B-RAF mutation received dasatinib, 140 mg, once daily as a tablet until unacceptable toxicity or disease progression occurred.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	BMS-354825
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dasatinib 50-mg and 20-mg tablets were administered orally as two tablets each taken once per day at the same time to receive a daily dose of 140 mg, until unacceptable toxicity or disease progression was observed by the investigator.

Arm title	Dasatinib, 140 mg (Squamous-cell NSCLC With DDR2 Mutation)

Arm description:

Subjects with NSCLC of squamous-cell type with DDR2 mutation received dasatinib, 140 mg, once daily as a tablet until unacceptable toxicity or disease progression occurred.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	BMS-354825
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dasatinib 50-mg and 20-mg tablets were administered orally as two tablets each taken once per day at the same time to receive a daily dose of 140 mg, until unacceptable toxicity or disease progression was observed by the investigator.

Number of subjects in period 1[1]	Dasatinib, 140 mg (NSCLC With Inactivating B-RAF Mutation)	Dasatinib, 140 mg (Squamous-cell NSCLC With DDR2 Mutation)
Started	9	5
Completed	0	0
Not completed	9	5
Disease progression	7	5
Study Drug Toxicity	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 19 subjects were enrolled and 14 received treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Dasatinib, 140 mg (NSCLC With Inactivating B-RAF Mutation)
Reporting group description:	
Subjects with non-small cell lung cancer (NSCLC) with inactivating B-RAF mutation received dasatinib, 140 mg, once daily as a tablet until unacceptable toxicity or disease progression occurred.	
Reporting group title	Dasatinib, 140 mg (Squamous-cell NSCLC With DDR2 Mutation)
Reporting group description:	
Subjects with NSCLC of squamous-cell type with DDR2 mutation received dasatinib, 140 mg, once daily as a tablet until unacceptable toxicity or disease progression occurred.	

Reporting group values	Dasatinib, 140 mg (NSCLC With Inactivating B-RAF Mutation)	Dasatinib, 140 mg (Squamous-cell NSCLC With DDR2 Mutation)	Total
Number of subjects	9	5	14
Age categorical Units: Subjects			
Adults (18-64 years)	3	3	6
From 65-84 years	6	2	8
Age continuous Units: years			
arithmetic mean	64.7	62.4	
standard deviation	± 8.23	± 9.21	-
Gender categorical Units: Subjects			
Female	5	1	6
Male	4	4	8
Race Units: Subjects			
White	8	4	12
Black or African American	0	1	1
American Indian or Alaska Native	1	0	1
Ethnicity Units: Subjects			
Hispanic/Latino	1	0	1
Not Hispanic/Latino	5	5	10
Not reported	3	0	3
Tumor Type Units: Subjects			
Non-small cell lung carcinoma	9	5	14
Non-small cell lung carcinoma Units: Subjects			
Adenocarcinoma	7	1	8
Bronco-alveolar carcinoma	1	0	1
Large cell carcinoma	1	0	1
Squamous cell carcinoma	0	4	4
Histopathologic Grade Units: Subjects			

G2-moderately differentiated	2	2	4
G3-poorly differentiated	2	0	2
GX-grade cannot be assessed	5	3	8
Baseline Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG is a 6-item scale used to assess disease progression, daily functioning, and appropriate treatment and prognosis. Performance status is scored on a scale ranging from 0-5, with (best score) 0=fully active and able to carry on all predisease performance without restriction and (worst score) 5=death.			
Units: Subjects			
Baseline ECOG score: 0	1	1	2
Baseline ECOG score: 1	6	3	9
Baseline ECOG score: 2	2	1	3
Number of Index Lesions Units: Subjects			
1 Lesion	2	1	3
2 Lesion	0	2	2
3 Lesion	4	1	5
4 Lesion	3	1	4
Time from cancer diagnosis to start of study therapy Units: Months			
median	14.4	8.5	
full range (min-max)	6.2 to 21.7	1.5 to 51.6	-

Subject analysis sets

Subject analysis set title	All treated subjects
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received at least 1 dose of study drug therapy during the study.

Reporting group values	All treated subjects		
Number of subjects	14		
Age categorical Units: Subjects			
Adults (18-64 years)	6		
From 65-84 years	8		
Age continuous Units: years			
arithmetic mean	63.9		
standard deviation	± 8.31		
Gender categorical Units: Subjects			
Female	6		
Male	8		
Race Units: Subjects			
White	12		
Black or African American	1		
American Indian or Alaska Native	1		
Ethnicity Units: Subjects			

Hispanic/Latino	1		
Not Hispanic/Latino	10		
Not reported	3		
Tumor Type Units: Subjects			
Non-small cell lung carcinoma	14		
Non-small cell lung carcinoma Units: Subjects			
Adenocarcinoma	8		
Bronco-alveolar carcinoma	1		
Large cell carcinoma	1		
Squamous cell carcinoma	4		
Histopathologic Grade Units: Subjects			
G2-moderately differentiated	4		
G3-poorly differentiated	2		
GX-grade cannot be assessed	8		
Baseline Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG is a 6-item scale used to assess disease progression, daily functioning, and appropriate treatment and prognosis. Performance status is scored on a scale ranging from 0-5, with (best score) 0=fully active and able to carry on all predisease performance without restriction and (worst score) 5=death.			
Units: Subjects			
Baseline ECOG score: 0	2		
Baseline ECOG score: 1	9		
Baseline ECOG score: 2	3		
Number of Index Lesions Units: Subjects			
1 Lesion	3		
2 Lesion	2		
3 Lesion	5		
4 Lesion	4		
Time from cancer diagnosis to start of study therapy Units: Months			
median	12.1		
full range (min-max)	1.5 to 51.6		

End points

End points reporting groups

Reporting group title	Dasatinib, 140 mg (NSCLC With Inactivating B-RAF Mutation)
Reporting group description:	
Subjects with non-small cell lung cancer (NSCLC) with inactivating B-RAF mutation received dasatinib, 140 mg, once daily as a tablet until unacceptable toxicity or disease progression occurred.	
Reporting group title	Dasatinib, 140 mg (Squamous-cell NSCLC With DDR2 Mutation)
Reporting group description:	
Subjects with NSCLC of squamous-cell type with DDR2 mutation received dasatinib, 140 mg, once daily as a tablet until unacceptable toxicity or disease progression occurred.	
Subject analysis set title	All treated subjects
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least 1 dose of study drug therapy during the study.	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]
End point description:	
ORR is defined as the percentage of subjects with best tumor response of either Partial Response (PR) (a 30% or greater decrease in the sum of the longest diameter [LD] of all lesions in reference to the baseline sum LD) or Complete Response (CR) (disappearance of clinical and radiologic evidence of target lesions), according to Response Evaluation Criteria in Solid Tumors. The analysis was performed in all treated and response evaluable subject who received at least 1 dose of study drug. Response-evaluable subjects are defined as all treated subjects with >=1 measurable tumor at baseline and >=1 on-study tumor assessment (or with >=1 measurable tumor at baseline and a Clinical Progressive Disease (cPD) recorded).	
End point type	Primary
End point timeframe:	
From enrollment of last subject to 24 months or until all subjects have died, whichever occurs first	

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: None of the subjects achieved ORR.

End point values	Dasatinib, 140 mg (NSCLC With Inactivating B-RAF Mutation)	Dasatinib, 140 mg (Squamous-cell NSCLC With DDR2 Mutation)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: Percentage of subjects				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response is defined as the time from the first assessment with documentation of partial or complete response until the first with assessment documentation of disease progression. The analysis was performed in all the subjects who received at least 1 dose of study drug. Here '99999' signifies not estimable data.

End point type	Secondary

End point timeframe:

From enrollment of last subject to 24 months or until all subjects have died, whichever occurs first

End point values	Dasatinib, 140 mg (NSCLC With Inactivating B-RAF Mutation)	Dasatinib, 140 mg (Squamous-cell NSCLC With DDR2 Mutation)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: Months				
number (not applicable)	99999	99999		

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 time from treatment start date to the date of death. If the subject did not die, survival was censored on the last date the subject was known to be alive. The analysis was performed in all the subjects who received at least 1 dose of the study drug. Here '99999' signifies not estimable data as the upper limit of the Brookmeyer-Crowley confidence interval could not be estimated.

End point type	Secondary

End point timeframe:

From enrollment of last subject to 24 months or until all subjects have died, whichever occurs first

End point values	Dasatinib, 140 mg (NSCLC With Inactivating B-RAF Mutation)	Dasatinib, 140 mg (Squamous-cell NSCLC With DDR2 Mutation)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: Months				
median (confidence interval 90%)	3.06 (0.76 to 6.47)	4.21 (0.82 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) Distribution

End point title	Progression-free Survival (PFS) Distribution

End point description:

PFS is defined as the time from treatment start date to the earliest evidence of disease progression or death. Subjects who did not progress or die were censored on the date of their last tumor assessment. Here -99999 to 99999 signifies that no confidence interval is applicable when all subjects progressed.

End point type	Secondary

End point timeframe:

From Day 1 of study treatment to Week 12

End point values	Dasatinib, 140 mg (NSCLC With Inactivating B-RAF Mutation)	Dasatinib, 140 mg (Squamous-cell NSCLC With DDR2 Mutation)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: Percentage of subjects				
number (confidence interval 90%)	13.3 (1.4 to 38.8)	0 (-99999 to 99999)		

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 is defined as the time from treatment start date to the earliest evidence of disease progression or death. Subjects who die or whose disease does not progress will be censored on the date of their last tumor assessment. The analysis was performed in all the subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From Day 1 of study treatment to Week 12

End point values	Dasatinib, 140 mg (NSCLC With Inactivating B-RAF Mutation)	Dasatinib, 140 mg (Squamous-cell NSCLC With DDR2 Mutation)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: Months				
median (confidence interval 90%)	1.41 (0.72 to 1.87)	1.38 (0.59 to 2.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Serious Adverse Events (SAEs), Drug-related SAEs, Adverse Events (AEs) Leading to Discontinuation, Drug-related AEs Leading to Discontinuation, and Deaths

End point title	Number of Subjects With Serious Adverse Events (SAEs), Drug-related SAEs, Adverse Events (AEs) Leading to Discontinuation, Drug-related AEs Leading to Discontinuation, and Deaths

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Drug-related=having certain, probable, possible, or unknown relationship to study drug. The analysis was performed in all the subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From enrollment of last subject to 24 months or until all subjects have died, whichever occurs first

End point values	Dasatinib, 140 mg (NSCLC With Inactivating B-RAF Mutation)	Dasatinib, 140 mg (Squamous-cell NSCLC With DDR2 Mutation)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: Subjects				
Death	8	4		
Death within 30 days of last treatment	3	1		
SAEs	7	4		
Drug-related SAEs	0	1		
AEs leading to discontinuation	7	2		

Drug-related AEs leading to discontinuation	2	0		
Drug-related AEs	6	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Testing Results That Meet the Criteria for Grade 3 or 4 Abnormality

End point title	Number of Subjects With Laboratory Testing Results That Meet the Criteria for Grade 3 or 4 Abnormality

End point description:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living. Grade 4: Life-threatening consequences; urgent intervention indicated. Grade 5: Death related to adverse event. Laboratory values graded by Common Terminology Criteria for Adverse Events, volume 3. Hemoglobin, Grade 3: <8.0 - 6.5 g/dL, <4.9-4.0 mmol/L, <80-65 g/L. Alkaline phosphatase, Grade 3: >5.0-20.0*upper limit of normal (ULN). Total bilirubin, Grade 3: >3.0-10.0*ULN. Calcium, low, Grade 3: <7.0-6.0 mg/dL, <1.75-1.5 mmol/L. The analysis was performed in all the subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From Day 1 of treatment to last day of treatment + 30 days

End point values	All treated subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: Subjects				
Hemoglobin, Grade 3	2			
Alkaline phosphatase, Grade 3	1			
Total bilirubin, Grade 3	1			
Calcium, low, Grade 3	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Day 1 of treatment to last day of treatment + 30 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	All Treated Subjects
Reporting group description:	
All subjects who received at least 1 dose of study drug therapy.	

Serious adverse events	All Treated Subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 14 (78.57%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 3		
Neoplasm malignant			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Non-small cell lung cancer			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Lipase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pleural effusion			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Panic reaction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All Treated Subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Vasculitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 14 (50.00%)		
occurrences (all)	7		
Oedema peripheral			

subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Chest pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Oedema			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Asthenia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Extravasation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	6 / 14 (42.86%)		
occurrences (all)	6		
Cough			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	4		
Pleural effusion			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	4		
Haemoptysis			

subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Dyspnoea exertional			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nasal ulcer			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Confusional state			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	4		
Blood albumin decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood alkaline phosphatase			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood glucose increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Calcium ionised increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Lipase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Neuropathy peripheral			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Parosmia			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Sedation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Eye disorders			
Eye disorder			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Eyelid oedema			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Uveitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 14 (35.71%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	4		
Vomiting			

subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pancreatitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Diverticular perforation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pruritus			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Urinary straining			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pain in jaw			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Groin pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Hypoalbuminaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Hypomagnesaemia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2012	The purpose of this amendment was to remove subjects suffering from malignant melanoma with inactivating B-RAF mutation from the study design and inclusion of local laboratories to perform B-RAF and discoidin domain receptor 2 (DDR2) mutation testing (pre-screening).
21 August 2013	The purpose of this amendment was to allow subjects with non-squamous cell carcinoma of the lung in the stratum of subjects suffering from non-small cell lung cancer with DDR2 mutation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated due to lack of efficacy and slow enrollment of subjects in the study.

Notes: