



Clinical trial results:

A Phase II study of the BRAF inhibitor dabrafenib as a single agent and in combination with the MEK inhibitor trametinib in subjects with BRAF V600E mutation positive metastatic (stage IV) non-small cell lung cancer Summary

EudraCT number	2011-001161-41
Trial protocol	GB NO DE ES NL IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	21 October 2016
First version publication date	21 October 2016

Trial information

Trial identification

Sponsor protocol code	113928
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	27 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2015
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the overall response rate (ORR) in subjects with stage IV BRAF V600E mutant non-small cell lung cancer administered dabrafenib as a single agent (Cohort A) and in combination with trametinib (Cohorts B and C)

Protection of trial subjects:

Participants in this study received supportive care according to standard medical practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	France: 57
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Netherlands: 22
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	166
EEA total number of subjects	104

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)	71
From 65 to 84 years	88
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Eligible participants (par.) were enrolled in Cohort (Coh) A (monotherapy [Dabrafenib{DAB}]). Par. in Coh-A who had disease progression and adequately tolerating DAB were given option to crossover to Coh-B who received combination therapy (DAB+Trametinib). In Coh-C, par. without prior anti-cancer treatment received combination therapy.

Pre-assignment

Screening details:

Par. with metastatic non-small cell lung cancer (NSCLC) were screened and allocated to Coh-A (DAB twice daily [BID] i.e. monotherapy), Coh-B (Combination Second-Line Plus) and Coh-C (Combination First-Line) according to their eligibility. The results presented are based on the Interim Analysis.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Monotherapy All Treated

Arm description:

Participants with or without prior systemic anti-cancer therapy received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Arm type	Experimental
Investigational medicinal product name	Product 1
Investigational medicinal product code	Dabrafenib (GSK2118436)
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

It will be provided as 50 mg and 75 mg hydroxypropyl methylcellulose (HPMC) capsules. Dabrafenib will be administered as a single agent in all cohorts.

Arm title	Combination Second-Line Plus
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Arm description:

Participants who had received 1-3 prior lines of systemic anti-cancer therapies received dabrafenib 150 mg BID and trametinib 2 mg once daily (OD). It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue.

Arm type	Experimental
Investigational medicinal product name	Product 1
Investigational medicinal product code	Trametinib (GSK1120212)
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

It will be provided as 0.5 mg and 2 mg tablets. Trametinib will be administered in combination with dabrafenib in Cohorts B and C

Arm title	Combination First-Line
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Arm description:

Participants who had not received any prior systemic anti-cancer therapies were given dabrafenib 150 mg BID and trametinib 2 mg OD. It was continued until disease progression or death or unacceptable

AEs or at investigator discretion to discontinue.

Arm type	Experimental
Investigational medicinal product name	Product 1
Investigational medicinal product code	Trametinib (GSK1120212)
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

It will be provided as 0.5 mg and 2 mg tablets. Trametinib will be administered in combination with dabrafenib in Cohorts B and C

Investigational medicinal product name	Product 1
Investigational medicinal product code	Dabrafenib (GSK2118436)
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

It will be provided as 50 mg and 75 mg hydroxypropyl methylcellulose (HPMC) capsules. Dabrafenib will be administered as a single agent in all cohorts.

Number of subjects in period 1	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line
Started	84	57	25
Completed	0	0	0
Not completed	84	57	25
Adverse event, serious fatal	57	23	1
Consent withdrawn by subject	6	-	-
Transferred to Other Arm/Group	8	-	-
Ongoing	10	32	24
Lost to follow-up	3	2	-

Baseline characteristics

Reporting groups

Reporting group title	Monotherapy All Treated
Reporting group description:	
Participants with or without prior systemic anti-cancer therapy received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.	
Reporting group title	Combination Second-Line Plus
Reporting group description:	
Participants who had received 1-3 prior lines of systemic anti-cancer therapies received dabrafenib 150 mg BID and trametinib 2 mg once daily (OD). It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue.	
Reporting group title	Combination First-Line
Reporting group description:	
Participants who had not received any prior systemic anti-cancer therapies were given dabrafenib 150 mg BID and trametinib 2 mg OD. It was continued until disease progression or death or unacceptable AEs or at investigator discretion to discontinue.	

Reporting group values	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line
Number of subjects	84	57	25
Age categorical			
Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	64.8	65.1	70.8
standard deviation	± 10.51	± 10.14	± 9.5
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	44	28	15
Male	40	29	10
Race/Ethnicity, Customized			
Units: Subjects			
Asian - East Asian Heritage	14	3	1
Asian - Central/South Asian Heritage	2	0	0
Asian - Japanese Heritage	2	1	0
African American/African Heritage	2	2	0
Native Hawaiian Or Other Pacific Islander	0	0	1
White - Arabic/North African Heritage	2	2	0
White - White/Caucasian/European Heritage	62	47	23
Other-African American/African Heritage	0	1	0
Other-missing	0	1	0

Reporting group values	Total		
Number of subjects	166		
Age categorical			
Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	87		
Male	79		
Race/Ethnicity, Customized			
Units: Subjects			
Asian - East Asian Heritage	18		
Asian - Central/South Asian Heritage	2		
Asian - Japanese Heritage	3		
African American/African Heritage	4		
Native Hawaiian Or Other Pacific Islander	1		
White - Arabic/North African Heritage	4		
White - White/Caucasian/European Heritage	132		
Other-African American/African Heritage	1		
Other-missing	1		

End points

End points reporting groups

Reporting group title	Monotherapy All Treated
Reporting group description: Participants with or without prior systemic anti-cancer therapy received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.	
Reporting group title	Combination Second-Line Plus
Reporting group description: Participants who had received 1-3 prior lines of systemic anti-cancer therapies received dabrafenib 150 mg BID and trametinib 2 mg once daily (OD). It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue.	
Reporting group title	Combination First-Line
Reporting group description: Participants who had not received any prior systemic anti-cancer therapies were given dabrafenib 150 mg BID and trametinib 2 mg OD. It was continued until disease progression or death or unacceptable AEs or at investigator discretion to discontinue.	
Subject analysis set title	Monotherapy Second-Line Plus
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with or without prior systemic anti-cancer therapy received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.	
Subject analysis set title	Combination Second-Line Plus
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who had received 1-3 prior lines of systemic anti-cancer therapies received dabrafenib 150 mg BID and trametinib 2 mg once daily (OD). It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue.	
Subject analysis set title	Combination First-Line
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who had not received any prior systemic anti-cancer therapies were given dabrafenib 150 mg BID and trametinib 2 mg OD. It was continued until disease progression or death or unacceptable AEs or at investigator discretion to discontinue.	

Primary: Percentage of participants with overall response rate (ORR) at the date of analysis

End point title	Percentage of participants with overall response rate (ORR) at the date of analysis ^{[1][2]}
End point description: ORR is defined as the percentage of par. with a confirmed complete response (CR) or partial response (PR) by investigator assessment as per Response Evaluation Criteria In Solid Tumors (RECIST) criteria version 1.1. RECIST criteria evaluates the response on the basis of target and non-target lesions, and best over all response. The response rate was analyzed every 6 weeks (wks) after initiation of study treatment until Week 36 and then every 12 wks. Percentage of par. analyzed as number of par. having overall response on the date of analysis from Baseline multiply by 100. The Second Line Plus All Treated Population used for cohort A and B consisted of all par. in the All Treated Population who had received at least one line of prior anti-cancer therapy for advanced/metastatic disease. The First-Line All Treated Population used for cohort C consisted of all par. in the All Treated Population who had not received any prior anti-cancer therapy for advanced/metastatic disease.	
End point type	Primary
End point timeframe: Arm 1: From First dose until 21-Nov-2014; Arm 2 and 3: From first dose until 07-Oct-2015.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis is available.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis is available.

End point values	Combination Second-Line Plus	Monotherapy Second-Line Plus	Combination First-Line	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	57 ^[3]	78	15	
Units: Percentage of Participants				
number (confidence interval 95%)	63.2 (49.3 to 75.6)	33.3 (23.1 to 44.9)	53.3 (26.6 to 78.7)	

Notes:

[3] - Second-Line All Treated Population for Coh-A and Coh-B / First-Line All Treated Population for Coh-C

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR) at the date of analysis

End point title	Duration of response (DoR) at the date of analysis ^[4]
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End point description:

DoR is defined for the subset of participants with confirmed CR or PR, as the time from first documented evidence of CR or PR until time of first documented disease progression or death due to any cause. The response was analyzed every 6 weeks after initiation of study treatment until Week 36 and then every 12 wks. Disease progression will be based on radiological assessments magnetic resonance imaging (MRI) or computed tomography (CT). Confidence Intervals estimated using the Brookmeyer Crowley method. Upper limit of confidence interval was not reached as data were not yet mature. The data for Cohort C is not posted as study is ongoing. Second-Line All Treated Population for Coh-A and Coh-B, and First-Line All Treated Population for Coh-C.

End point type	Secondary
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End point timeframe:

Arm 1: From First dose until 21-Nov-2014; Arm 2 and 3: From first dose until 07-Oct-2015

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis is available.

End point values	Combination Second-Line Plus	Monotherapy Second-Line Plus	Combination First-Line	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	36	26	0 ^[5]	
Units: Months				
median (confidence interval 95%)	9 (6.9 to 18.3)	9.6 (5.4 to 15.2)	(to)	

Notes:

[5] - The data for Cohort C is not posted as study is ongoing.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) at the date of analysis

End point title	Progression free survival (PFS) at the date of analysis
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End point description:

PFS is defined as the interval between first dose and the earliest date of disease progression or death due to any cause. The target and non-target lesions were identified at time of screening and the same lesions were re-assessed by a contrast-enhanced brain magnetic resonance imaging or Computed tomography every 6 wks after initiation of study treatment until Week 36 and then every 12 wks. Confidence Intervals estimated using the Brookmeyer Crowley method. The data for Cohort C is not posted as study is ongoing. First-Line Second-Line All Treated Population for Coh-A and Coh-B, and First-Line All Treated Population for Coh-C.

End point type	Secondary
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End point timeframe:

Arm 1: From First dose until 21-Nov-2014; Arm 2 and 3: From first dose until 07-Oct-2015

End point values	Monotherapy Second-Line Plus	Combination Second-Line Plus	Combination First-Line	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	78	57	0 ^[6]	
Units: Months				
median (confidence interval 95%)	5.5 (3.4 to 7.3)	9.7 (6.9 to 19.6)	(to)	

Notes:

[6] - The data for Cohort C is not posted as study is ongoing.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) at the date of analysis

End point title	Overall survival (OS) at the date of analysis ^[7]
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End point description:

OS defined as the time from first dose until death due to any cause. Confidence Intervals estimated using the Brookmeyer Crowley method. The data for Cohort C is not posted as study is ongoing. A value of "99999" indicates where no data is available or not able to determine the value. First-Line Second-Line All Treated Population for Coh-A and Coh-B, and First-Line All Treated Population for Coh-C.

End point type	Secondary
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End point timeframe:

Arm 1 and 2: From First dose until 07-Oct-2015

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No statistical analysis is available.

End point values	Combination Second-Line Plus	Monotherapy Second-Line Plus	Combination First-Line	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	78	0 ^[8]	
Units: Months				
median (confidence interval 95%)	17.6 (14.3 to 99999)	12.7 (7.3 to 16.3)	(to)	

Notes:

[8] - The data for Cohort C is not posted as study is ongoing.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events will be collected from time the first study dose is administered until 30 days following discontinuation of study treatment.

Adverse event reporting additional description:

Adverse events will be graded according to the common terminology criteria for adverse events (CTCAE), version 4. For participants in the Crossover Population, any treatment-emergent AEs related to the initiation of combination treatment will be summarized for Crossover Population only.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Monotherapy
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Reporting group description:

Participants with or without prior systemic anti-cancer therapy received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Reporting group title	Combination Therapy
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Reporting group description:

Combination of participants who had received 1-3 prior lines of systemic anti-cancer therapies and participants who had not received any prior systemic anti-cancer therapies received dabrafenib 150 mg BID and trametinib 2 mg once daily (OD). It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue.

Serious adverse events	Monotherapy	Combination Therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 84 (42.86%)	38 / 82 (46.34%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	4 / 84 (4.76%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			

subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip squamous cell carcinoma			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Squamous cell carcinoma			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	8 / 84 (9.52%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	8 / 8	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 84 (1.19%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 84 (1.19%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 84 (1.19%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	1 / 84 (1.19%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	5 / 84 (5.95%)	10 / 82 (12.20%)	
occurrences causally related to treatment / all	3 / 6	9 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 84 (1.19%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 84 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 84 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 84 (1.19%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 84 (1.19%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 84 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	2 / 84 (2.38%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
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			
Incisional hernia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			

subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
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	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transient ischaemic attack			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 84 (0.00%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic thrombosis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal dystrophy			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis ischaemic			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (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	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 84 (1.19%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			
subjects affected / exposed	1 / 84 (1.19%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery thrombosis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal failure			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 84 (1.19%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Influenza			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Legionella infection			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 84 (2.38%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 84 (2.38%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	1 / 84 (1.19%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 84 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Monotherapy	Combination Therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 84 (97.62%)	77 / 82 (93.90%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Keratoacanthoma			
subjects affected / exposed	6 / 84 (7.14%)	0 / 82 (0.00%)	
occurrences (all)	6	0	

Acrochordon			
subjects affected / exposed	5 / 84 (5.95%)	0 / 82 (0.00%)	
occurrences (all)	5	0	
Melanocytic naevus			
subjects affected / exposed	9 / 84 (10.71%)	2 / 82 (2.44%)	
occurrences (all)	12	3	
Papilloma			
subjects affected / exposed	6 / 84 (7.14%)	0 / 82 (0.00%)	
occurrences (all)	6	0	
Seborrhoeic keratosis			
subjects affected / exposed	8 / 84 (9.52%)	2 / 82 (2.44%)	
occurrences (all)	10	2	
Skin papilloma			
subjects affected / exposed	23 / 84 (27.38%)	1 / 82 (1.22%)	
occurrences (all)	40	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 84 (5.95%)	3 / 82 (3.66%)	
occurrences (all)	6	3	
Hypotension			
subjects affected / exposed	6 / 84 (7.14%)	7 / 82 (8.54%)	
occurrences (all)	6	8	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	25 / 84 (29.76%)	18 / 82 (21.95%)	
occurrences (all)	31	20	
Chest pain			
subjects affected / exposed	6 / 84 (7.14%)	5 / 82 (6.10%)	
occurrences (all)	7	6	
Chills			
subjects affected / exposed	12 / 84 (14.29%)	15 / 82 (18.29%)	
occurrences (all)	15	20	
Fatigue			
subjects affected / exposed	25 / 84 (29.76%)	14 / 82 (17.07%)	
occurrences (all)	27	16	
Malaise			

subjects affected / exposed	5 / 84 (5.95%)	5 / 82 (6.10%)	
occurrences (all)	5	6	
Oedema			
subjects affected / exposed	2 / 84 (2.38%)	5 / 82 (6.10%)	
occurrences (all)	2	6	
Mucosal inflammation			
subjects affected / exposed	5 / 84 (5.95%)	3 / 82 (3.66%)	
occurrences (all)	6	4	
Oedema peripheral			
subjects affected / exposed	3 / 84 (3.57%)	19 / 82 (23.17%)	
occurrences (all)	7	24	
Pain			
subjects affected / exposed	2 / 84 (2.38%)	5 / 82 (6.10%)	
occurrences (all)	2	5	
Pyrexia			
subjects affected / exposed	29 / 84 (34.52%)	33 / 82 (40.24%)	
occurrences (all)	43	81	
Xerosis			
subjects affected / exposed	7 / 84 (8.33%)	4 / 82 (4.88%)	
occurrences (all)	7	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 84 (28.57%)	14 / 82 (17.07%)	
occurrences (all)	30	15	
Dysphonia			
subjects affected / exposed	8 / 84 (9.52%)	1 / 82 (1.22%)	
occurrences (all)	8	1	
Dyspnoea			
subjects affected / exposed	17 / 84 (20.24%)	11 / 82 (13.41%)	
occurrences (all)	19	12	
Haemoptysis			
subjects affected / exposed	7 / 84 (8.33%)	4 / 82 (4.88%)	
occurrences (all)	7	4	
Productive cough			

subjects affected / exposed occurrences (all)	6 / 84 (7.14%) 6	6 / 82 (7.32%) 8	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	6 / 84 (7.14%) 6	6 / 82 (7.32%) 6	
Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all)	5 / 84 (5.95%) 5 15 / 84 (17.86%) 15 0 / 84 (0.00%) 0	8 / 82 (9.76%) 9 9 / 82 (10.98%) 10 7 / 82 (8.54%) 7	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	7 / 84 (8.33%) 7 4 / 84 (4.76%) 4 16 / 84 (19.05%) 18	8 / 82 (9.76%) 9 6 / 82 (7.32%) 8 10 / 82 (12.20%) 15	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia	10 / 84 (11.90%) 11 6 / 84 (7.14%) 7 2 / 84 (2.38%) 2	8 / 82 (9.76%) 9 2 / 82 (2.44%) 2 11 / 82 (13.41%) 24	

subjects affected / exposed occurrences (all)	5 / 84 (5.95%) 5	4 / 82 (4.88%) 5	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	5 / 82 (6.10%) 9	
Eye disorders Vision blurred subjects affected / exposed occurrences (all) Visual acuity reduced subjects affected / exposed occurrences (all)	5 / 84 (5.95%) 5 3 / 84 (3.57%) 3	1 / 82 (1.22%) 3 5 / 82 (6.10%) 6	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting	8 / 84 (9.52%) 10 2 / 84 (2.38%) 2 9 / 84 (10.71%) 9 16 / 84 (19.05%) 22 1 / 84 (1.19%) 1 2 / 84 (2.38%) 2 24 / 84 (28.57%) 31	3 / 82 (3.66%) 3 7 / 82 (8.54%) 10 13 / 82 (15.85%) 15 22 / 82 (26.83%) 37 5 / 82 (6.10%) 5 6 / 82 (7.32%) 6 32 / 82 (39.02%) 49	

subjects affected / exposed	18 / 84 (21.43%)	23 / 82 (28.05%)	
occurrences (all)	26	54	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	10 / 84 (11.90%)	4 / 82 (4.88%)	
occurrences (all)	17	4	
Alopecia			
subjects affected / exposed	18 / 84 (21.43%)	5 / 82 (6.10%)	
occurrences (all)	18	5	
Dry skin			
subjects affected / exposed	21 / 84 (25.00%)	19 / 82 (23.17%)	
occurrences (all)	23	22	
Erythema			
subjects affected / exposed	1 / 84 (1.19%)	5 / 82 (6.10%)	
occurrences (all)	1	6	
Hair texture abnormal			
subjects affected / exposed	7 / 84 (8.33%)	3 / 82 (3.66%)	
occurrences (all)	7	3	
Madarosis			
subjects affected / exposed	5 / 84 (5.95%)	0 / 82 (0.00%)	
occurrences (all)	5	0	
Hyperkeratosis			
subjects affected / exposed	25 / 84 (29.76%)	6 / 82 (7.32%)	
occurrences (all)	55	6	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	19 / 84 (22.62%)	3 / 82 (3.66%)	
occurrences (all)	22	4	
Papule			
subjects affected / exposed	8 / 84 (9.52%)	2 / 82 (2.44%)	
occurrences (all)	8	2	
Pruritus			
subjects affected / exposed	12 / 84 (14.29%)	10 / 82 (12.20%)	
occurrences (all)	12	16	
Rash			

subjects affected / exposed	16 / 84 (19.05%)	15 / 82 (18.29%)	
occurrences (all)	16	21	
Rash maculo-papular			
subjects affected / exposed	5 / 84 (5.95%)	0 / 82 (0.00%)	
occurrences (all)	5	0	
Rash papular			
subjects affected / exposed	6 / 84 (7.14%)	3 / 82 (3.66%)	
occurrences (all)	6	3	
Skin lesion			
subjects affected / exposed	5 / 84 (5.95%)	2 / 82 (2.44%)	
occurrences (all)	8	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 84 (19.05%)	12 / 82 (14.63%)	
occurrences (all)	25	14	
Muscle spasms			
subjects affected / exposed	2 / 84 (2.38%)	6 / 82 (7.32%)	
occurrences (all)	2	7	
Back pain			
subjects affected / exposed	10 / 84 (11.90%)	7 / 82 (8.54%)	
occurrences (all)	11	9	
Muscular weakness			
subjects affected / exposed	6 / 84 (7.14%)	1 / 82 (1.22%)	
occurrences (all)	7	1	
Musculoskeletal pain			
subjects affected / exposed	5 / 84 (5.95%)	2 / 82 (2.44%)	
occurrences (all)	7	2	
Myalgia			
subjects affected / exposed	12 / 84 (14.29%)	9 / 82 (10.98%)	
occurrences (all)	15	12	
Pain in extremity			
subjects affected / exposed	15 / 84 (17.86%)	3 / 82 (3.66%)	
occurrences (all)	17	3	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	9 / 84 (10.71%)	5 / 82 (6.10%)	
occurrences (all)	10	7	
Bronchitis			
subjects affected / exposed	6 / 84 (7.14%)	5 / 82 (6.10%)	
occurrences (all)	7	8	
Rhinitis			
subjects affected / exposed	5 / 84 (5.95%)	5 / 82 (6.10%)	
occurrences (all)	6	6	
Upper respiratory tract infection			
subjects affected / exposed	7 / 84 (8.33%)	1 / 82 (1.22%)	
occurrences (all)	7	1	
Urinary tract infection			
subjects affected / exposed	5 / 84 (5.95%)	6 / 82 (7.32%)	
occurrences (all)	6	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	23 / 84 (27.38%)	19 / 82 (23.17%)	
occurrences (all)	30	21	
Hyperglycaemia			
subjects affected / exposed	5 / 84 (5.95%)	3 / 82 (3.66%)	
occurrences (all)	6	4	
Hypokalaemia			
subjects affected / exposed	5 / 84 (5.95%)	5 / 82 (6.10%)	
occurrences (all)	8	5	
Hyponatraemia			
subjects affected / exposed	3 / 84 (3.57%)	7 / 82 (8.54%)	
occurrences (all)	4	9	
Hypophosphataemia			
subjects affected / exposed	6 / 84 (7.14%)	5 / 82 (6.10%)	
occurrences (all)	11	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2011	Updated the inclusion / exclusion criteria, updated the QTc withdrawal criteria and the Dose Modification section, added an Independent Data Monitoring Committee. In addition, language specific to French sites was added. Throughout the protocol, minor administrative and typographical changes were made.
13 October 2011	Increased the frequency of cardiac monitoring from every 12 weeks to every 9 weeks. Other clarifications to the PGx sections in the main text and in Appendix 1, description of physical exam and list of laboratory tests were made. Guidelines for management of renal insufficiency were added. A baseline sample for cytokine profiling was added (in the event a subject develops fever, the baseline cytokine values are available).
30 April 2012	Is a country specific amendment that changed the QTc stopping criteria to 500 msec for UK subjects and clarified the definition of abstinence
15 June 2012	Changed Inclusion to clarify that the failed chemotherapy regimen must have been a platinum-based chemotherapy; changed Exclusion Criteria #9 regarding the length of time a subject must be disease free from 5 years to 3 years; allowed for continued treatment with GSK2118436 beyond disease progression; updated the Dose Modification Guidelines for Fever and the Renal Insufficiency Guidelines for consistency with the current asset-specific language; added the UK to Appendix 3 (country-specific QTc stopping criteria of 500 msec); clarified restrictions on certain foods known to affect drug metabolism; clarified when an MRI or CT is required at baseline and on-study; removed the requirement for males who choose abstinence as their contraceptive method to begin abstinence 14 days BEFORE administration of GSK2118436; clarified the definition of abstinence; fixed T&E footnotes, lessened the frequency of efficacy assessments beginning at Week 36 and onwards, and removed the ANC measurement on Day 8; clarified SAE language for consistency with current asset language.
20 August 2012	Updated the Background section (Section 1.1) to include the currently available safety and efficacy data for GSK2118436; changed Inclusion Criterion (#7) to clarify for the reader that additional details on mutation testing and central confirmation of mutation testing are provided in Section 7.1.1; changes to Section 7.1.1 included clarification on BRAF mutation testing and intent that all subject have tissue available for central confirmation (when testing at inclusion is performed at a local laboratory) (also affected T&E footnote); removed the requirement for men to use contraception (Inclusion Criterion #9 and Section 7.4.2); changed the limit for use of anti-cancer treatment prior to dosing with GSK2118436 from 28 days to 14 days (Exclusion Criteria #2 and #3); added defined safety and efficacy criteria that need to be met in order to allow treatment with GSK2118436 beyond disease progression (Section 4.2.1); updated Section 5.7, Guidelines for Dose Modification and Events of Special Interest, in line with current asset language; clarified QTc Stopping Criteria to delineate QTcF v QTcB and QTc uncorrected stopping values; and clarified protocol-specific SAE language for consistency with current asset language (removed LVEF stopping criteria as a protocol specific SAE).
24 January 2013	Is a country specific amendment for France and the UK that specifies QTc stopping criteria in Appendix 3. Footnotes to the Time and Events Table were also renumbered.

16 April 2013	Added the study expansion cohort (n=20) increasing total sample size to 60 subjects, updated the eligibility criteria to remove the requirement of disease progression on a platinum-based chemotherapy prior to study enrollment to allow inclusion of first line metastatic patients in the expansion cohort and allow subjects with HCV clearance, updated QTc stopping criteria, removed herbal remedies as a prohibitive medication (St Johns Wort still prohibited), updated the prohibitive and cautionary medication list, increased the frequency of dermatologic assessments to every 9 weeks, changed blood sample for cfDNA at disease progression from optional to required, replaced "GSK2118436" with "dabrafenib" throughout the document and additional administrative level clarifications and edits. Section 1.2.1 deleted, please refer to the Dabrafenib Investigator's Brochure for all background/clinical trial information on dabrafenib.
25 September 2013	Added the dabrafenib/trametinib combination therapy cohort (n=40) increasing the total sample size to 100 subjects, ophthalmic examination added at screening, Week 6 and as clinically necessary thereafter for combination treatment only, combination cohort specific inclusion/exclusion criteria added, combination cohort specific dose modification and toxicity management guidelines added, option to crossover from monotherapy to combination treatment at time of radiologic disease progression added, ECHO and ECG schedule clarified as baseline, Week 6 and every 9 weeks thereafter
14 October 2014	Updated secondary medical monitor. Added Cohort C to enroll 25 first line subjects. Additional language added to study rationale in Section 1.2.1. Revised required laboratory value for PT/INR and PTT in Section 4.1.2. Removed HIV from ExclusionCriterion #7 and revised Exclusion Criterion #15 in Section 4.1.3. Additional language added to Section 4.2.1 and Section 4.2.3 to clarify requirements for continuing study treatment post-PD and for crossover requirements. Updated dose modification and toxicity management language throughout Section 5.9. Updated general dose modification guidelines in Section 5.9.2. Updated dose modification guidelines and stopping criteria for LVEF in Section 5.10.1. Updated liver chemistry stopping and follow-up criteria in Section 5.10.3. Guidelines for holding study drug following radiation treatment added to Section 6.1. Specified that body fluid sample (e.g., pleural effusion) is not acceptable for BRAF mutation testing sample in Section 7.1.1. Added confirmation of measurable disease by independent review at baseline prior to enrolment in Section 7.1.2. Updated language regarding ophthalmic examination requirements in Section 7.3.2.3. Added language in Section 7.3.2.9.2 allowing investigator to decide if basal cell carcinoma should be reported as SAE or not. Specified in Section 7.4.1 that females should wait at least 4 months after last dose of the combination therapy before nursing. Specified in Section 7.7 that body fluid sample (e.g., pleural effusion) is not preferred for PD biomarker sample. Added Section 9.1.3 to describe hypothesis and study design for Cohort C. Updated Section 9.2 regarding Cohort C. Updated Investigator Brochures citations to current versions. Appendix 4 added regarding additional monitoring requirements for subjects in France only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported