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	v2
This version publication date	18 August 2017
First version publication date	21 October 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	113928

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	09 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2016
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	Safety, Efficacy
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: 59
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Netherlands: 26
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	177
EEA total number of subjects	112

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)	79
From 65 to 84 years	90
85 years and over	8

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	Dabrafenib (GSK2118436)
Investigational medicinal product code	
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

Arm description:

Participants who had received 1-3 prior lines of systemic anti-cancer therapies for advanced stage/metastatic disease 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	Dabrafenib (GSK2118436)
Investigational medicinal product code	
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

Investigational medicinal product name	Trametinib (GSK1120212)
Investigational medicinal product code	
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

Arm description:

Participants who had not received any prior systemic anti-cancer for metastatic disease 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	Dabrafenib (GSK2118436)
Investigational medicinal product code	
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

Investigational medicinal product name	Trametinib (GSK1120212)
Investigational medicinal product code	
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

Number of subjects in period 1	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line
Started	84	57	36
Completed	0	0	0
Not completed	84	57	36
Adverse event, serious fatal	60	33	10
Consent withdrawn by subject	6	-	1
Physician decision	1	1	-
Ongoing	15	22	24
Lost to follow-up	2	1	1

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 for advanced stage/metastatic disease 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 for metastatic disease 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	36
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	64.8	65.1	67.8
standard deviation	± 10.51	± 10.14	± 11
Gender categorical			
Units: Subjects			
Female	44	28	22
Male	40	29	14
Race/Ethnicity, Customized			
Units: Subjects			
Asian - East Asian Heritage	14	3	3
Asian - Central/South Asian Heritage	2	0	0
Asian - Japanese Heritage	2	1	0
African American/African Heritage	2	2	1
Native Hawaiian Or Other Pacific Islander	0	0	1
White - Arabic/North African Heritage	2	2	0
White - White/Caucasian/European Heritage	62	47	30
Other-African American/African Heritage	0	1	0
Other-missing	0	1	1

Reporting group values	Total		

Number of subjects	177		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	94		
Male	83		
Race/Ethnicity, Customized Units: Subjects			
Asian - East Asian Heritage	20		
Asian - Central/South Asian Heritage	2		
Asian - Japanese Heritage	3		
African American/African Heritage	5		
Native Hawaiian Or Other Pacific Islander	1		
White - Arabic/North African Heritage	4		
White - White/Caucasian/European Heritage	139		
Other-African American/African Heritage	1		
Other-missing	2		

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 for advanced stage/metastatic disease 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 for metastatic disease 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 who have relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

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 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 until discharge or crossover. 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:

At Week 6 then every 6 weeks up to Week 36.and then every 12 weeks until discharge

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: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Combination Second-Line Plus	Combination First-Line	monotherapy second-line plus	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57[3]	36[4]	78[5]	
Units: Percentage of Participants				
number (confidence interval 95%)				
Percentage of Participants	66.7 (52.9 to 78.6)	61.1 (43.5 to 76.9)	33.3 (23.1 to 44.9)	

Notes:

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

[4] - Second-Line All Treated Population for Coh-A and Coh-B, First-Line All Treated Population for Coh-C

[5] - 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[6]

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 (CIs) estimated using the Brookmeyer Crowley method. Upper limit of confidence interval was not reached as data were not yet mature. A value of 99999 indicates where no data is available or not able to determine the value for Arm 3 due to a low event rate in that population (27 percent).

End point type	Secondary

End point timeframe:

At Week 6 then every 6 weeks up to Week 36.and then every 12 weeks until discharge

Notes:

[6] - 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: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Combination Second-Line Plus	Combination First-Line	monotherapy second-line plus	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57[7]	36[8]	78[9]	
Units: Months				
median (confidence interval 95%)				
Months	9.8 (6.9 to 16)	99999 (8.3 to 99999)	9.6 (5.4 to 15.2)	

Notes:

[7] - Second-Line All Treated Population for Coh-A, Coh-B, and First-Line All Treated Population for Coh-C

[8] - Second-Line All Treated Population for Coh-A, Coh-B, and First-Line All Treated Population for Coh-C

[9] - Second-Line All Treated Population for Coh-A, Coh-B, and First-Line All Treated Population for Coh-C

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[10]

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 (MRI) or Computed tomography (CT) every 6 wks after initiation of study treatment until Week 36 and then every 12 wks. CI estimated using the Brookmeyer Crowley method. A value of 99999 indicates where no data is available or not able to determine the value for Arm 3 due to a low event rate in the population (36 percent).

End point type	Secondary

End point timeframe:

At Week 6 then every 6 weeks up to Week 36.and then every 12 weeks until discharge

Notes:

[10] - 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: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Combination Second-Line Plus	Combination First-Line	monotherapy second-line plus	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57[11]	36[12]	78[13]	
Units: Months				
median (confidence interval 95%)				
Months	10.2 (6.9 to 16.7)	99999 (7 to 99999)	5.5 (3.4 to 7.3)	

Notes:

[11] - Second-Line All Treated Population for Coh-A, Coh-B, and First-Line All Treated Population for Coh-C
[12] - Second-Line All Treated Population for Coh-A, Coh-B, and First-Line All Treated Population for Coh-C
[13] - Second-Line All Treated Population for Coh-A, Coh-B, and First-Line All Treated Population for Coh-C

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[14]

End point description:

OS defined as the time from first dose until death due to any cause. CI estimated using the Brookmeyer Crowley method. A value of 99999 indicates where no data is available or not able to determine the value. The upper bound of the 95 percent CI for the median was not reached due to insufficient event rates for Arm 2 (58 percent) and Arm 3 (28 percent).

End point type	Secondary

End point timeframe:

At Week 6 then every 6 weeks up to Week 36.and then every 12 weeks until discharge

Notes:

[14] - 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: This endpoint is only reporting on a subset of the arms that are contained in the baseline

period.

End point values	Combination Second-Line Plus	Combination First-Line	monotherapy second-line plus	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57[15]	36[16]	78[17]	
Units: Months				
median (confidence interval 95%)				
Months	18.2 (14.3 to 99999)	24.6 (11.7 to 99999)	12.7 (7.3 to 16.3)	

Notes:

[15] - Second-Line All Treated Population for Coh-A, Coh-B, and First-Line All Treated Population for Coh-C

[16] - Second-Line All Treated Population for Coh-A, Coh-B, and First-Line All Treated Population for Coh-C

[17] - Second-Line All Treated Population for Coh-A, Coh-B, and First-Line All Treated Population for Coh-C

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal vital signs values

End point title	Number of participants with abnormal vital signs values

End point description:

Number of participants with abnormal values of vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate and temperature were evaluated. Participants with worst case post-Baseline vital sign values were presented at the given timepoints. Only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles). All treated population was used for monotherapy cohort which comprised of all participants in the monotherapy cohort who receive at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to Week 12 and then every 3 weeks until discharge

End point values	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[18]	57[19]	36[20]	
Units: Participants				
Heart rate; decrease to <60; n= 83, 56, 35	9	10	8	
Heart rate; increase to >100; n= 83, 56, 35	22	17	8	
SBP; grade 0 to 0; n= 83,56, 35	13	1	2	
SBP; grade 0 to 1; n= 83, 56, 35	11	9	7	
SBP; grade 0 to 2; n= 83, 56, 35	3	4	4	
SBP; grade 0 to 3; n= 83, 56, 35	2	0	2	
SBP; grade 1 to 0; n= 83, 56, 35	5	0	1	
SBP; grade 1 to 1; n= 83, 56, 35	13	10	1	

SBP; grade 1 to 2; n= 83, 56, 35	13	13	5	
SBP; grade 1 to 3; n= 83, 56, 35	4	6	5	
SBP; grade 2 to 0; n= 83, 56, 35	2	0	0	
SBP; grade 2 to 1; n= 83, 56, 35	1	1	0	
SBP; grade 2 to 2; n= 83, 56, 35	6	4	2	
SBP; grade 2 to 3; n= 83, 56, 35	6	5	3	
SBP; grade 3 to 0; n= 83, 56, 35	1	0	0	
SBP; grade 3 to 1; n= 83, 56, 35	0	0	0	
SBP; grade 3 to 2; n= 83, 56, 35	0	1	0	
SBP; grade 3 to 3; n= 83, 56, 35	3	2	3	
DBP; grade 0 to 0; n= 83, 56, 35	28	4	19	
DBP; grade 0 to 1; n= 83, 56, 35	15	12	9	
DBP; grade 0 to 2; n= 83, 56, 35	4	6	3	
DBP; grade 0 to 3; n= 83, 56, 35	3	5	1	
DBP; grade 1 to 0; n= 83, 56, 35	3	0	0	
DBP; grade 1 to 1; n= 83, 56, 35	11	6	1	
DBP; grade 1 to 2; n= 83, 56, 35	5	12	1	
DBP; grade 1 to 3; n= 83, 56, 35	3	5	1	
DBP; grade 2 to 0; n= 83, 56, 35	3	0	0	
DBP; grade 2 to 1; n= 83, 56, 35	1	0	0	
DBP; grade 2 to 2; n= 83, 56, 35	4	2	0	
DBP; grade 2 to 3; n= 83, 56, 35	1	3	0	
DBP; grade 3 to 0; n= 83, 56, 35	0	0	0	
DBP; grade 3 to 1; n= 83, 56, 35	0	0	0	
DBP; grade 3 to 2; n= 83, 56, 35	1	1	0	
DBP; grade 3 to 3; n= 83, 56, 35	1	0	0	
Temperature; decrease to <=35; n= 82, 56, 35	2	4	3	
Temperature; increase to >=38; n= 82, 56, 35	20	15	14	

Notes:

[18] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

[19] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

[20] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal electrocardiogram (ECG) values

End point title	Number of participants with abnormal electrocardiogram (ECG) values

End point description:

Single measurements of 12-lead ECGs were obtained at given time points using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and corrected QT (QTc) interval. ECG values at worst case post-Baseline were categorized as 'clinically significant change from Baseline' and 'not a clinically significant change'.

End point type	Secondary

End point timeframe:

Week 3, Week 6, Week 15 and then every 9 weeks until discharge

End point values	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80[21]	56[22]	35[23]	
Units: Participants				
Clinically significant	3	1	1	
Not clinically significant	77	55	34	

Notes:

[21] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

[22] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

[23] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal echocardiogram findings

End point title	Number of participants with abnormal echocardiogram findings

End point description:

Echocardiography scans were obtained at given time points using an echocardiogram and the findings for left ventricular ejection fraction (LVEF) were obtained. LVEF values at worst case post-Baseline were recorded as any increase and any decrease values.

End point type	Secondary

End point timeframe:

Week 6, Week 15 and then every 9 weeks until discharge

End point values	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77[24]	50[25]	32[26]	
Units: Participants				
Any increase	14	5	5	
Any decrease	51	39	20	
No change	12	6	7	

Notes:

[24] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

[25] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

[26] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal clinical chemistry values

End point title	Number of participants with abnormal clinical chemistry values

End point description:

Blood samples were collected from participants for evaluation of clinical chemistry parameters by worst case post-Baseline increase. The clinical chemistry parameters included creatinine, phosphate and high and low calcium, glucose, magnesium, potassium and sodium. Participants were counted in the category that their values shows any grade increase , Only those participants with data available at the specified

data points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Up to Week 12 and then every 3 weeks until discharge

End point values	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[27]	57[28]	36[29]	
Units: Participants				
Calcium high;n=80,55, 35	9	7	0	
Calcium, low;n=80,55,35	10	8	7	
Creatinine;n=80,55,35	8	11	6	
Glucose high;n=80, 55,35	54	40	24	
Glucose low;n=80, 55,35	9	9	4	
Magnesium high; n=80, 55,35	1	1	4	
Magnesium low; n= 80, 55,35	9	9	1	
Phosphate; n= 81,55,35	19	16	15	
Potassium high; n= 80,55,35	2	4	1	
Potassium low; n= 80,55,35	13	7	5	
Sodium high; n= 80, 55,35	4	1	0	
Sodium low; n= 80, 55,35	18	36	17	

Notes:

[27] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

[28] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

[29] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal hematology values

End point title	Number of participants with abnormal hematology values

End point description:

Blood samples were collected from participants for evaluation of hematology parameters by worst case post-Baseline increase. The hematology parameters included leukocytes, neutrophils, platelets and high and low hemoglobin and lymphocytes. Participants were counted in the category that their values shows any grade increase , Only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Up to Week 12 and then every 3 weeks until discharge

End point values	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[30]	57[31]	36[32]	
Units: Participants				
Hemoglobin high; n= 81,56,35	1	0	0	
Hemoglobin low; n= 81, 56,35	28	31	18	
Leukocytes; n= 82, 56,35	17	27	16	
Lymphocytes high; n= 82, 56,35	3	2	0	
Lymphocytes low; n= 82, 56,35	21	18	16	
Neutrophils; n= 82, 56,35	10	25	13	
Platelets; n= 81,56,35	5	11	4	

Notes:

[30] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

[31] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

[32] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with AEs and serious AEs (SAEs)

End point title	Number of participants with AEs and serious AEs (SAEs)

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. SAE is defined as any untoward medical occurrence that, at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability, is a congenital anomaly/ birth effect, other situations and is associated with liver injury or impaired liver function.

End point type	Secondary

End point timeframe:

Up to Week 12 and then every 3 weeks up to follow up

End point values	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[33]	57[34]	36[35]	
Units: Participants				
Any AE	83	56	36	
Any SAE	37	35	21	

Notes:

[33] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

[34] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

[35] - All treated Population for Coh- A,Second line All Treated for Coh-B, First Line All treated for CohC

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent clearance (CL/F) of Dabrafenib and trametinib

End point title	Apparent clearance (CL/F) of Dabrafenib and trametinib

End point description:

Blood samples from participants were collected for pharmacokinetic analysis including CL/F following oral dosing of dabrafenib and trametinib.

End point type	Secondary

End point timeframe:

Week 3, Week 6, Week 12 and Week 18

End point values	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[36]	0[37]	0[38]	
Units: Liter/day				
arithmetic mean (standard error)				
Liter/day	()	()	()	

Notes:

[36] - No data was analyzed

[37] - No data was analyzed

[38] - No data was analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of distribution (V/F) of Dabrafenib and trametinib

End point title	Volume of distribution (V/F) of Dabrafenib and trametinib

End point description:

Blood samples from participants were collected for pharmacokinetic analysis including V/F following oral dosing of dabrafenib and trametinib.

End point type	Secondary

End point timeframe:

Week 3, Week 6, Week 12 and Week 18

End point values	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[39]	0[40]	0[41]	
Units: Liter				
arithmetic mean (standard error)				
Liter	()	()	()	

Notes:

[39] - No data was analyzed

[40] - No data was analyzed

[41] - No data was analyzed

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

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 for advanced stage/metastatic disease 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 for metastatic disease 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.

Serious adverse events	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 84 (44.05%)	35 / 57 (61.40%)	21 / 36 (58.33%)
number of deaths (all causes)	1	7	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoma benign			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	4 / 84 (4.76%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	3 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratoacanthoma			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip squamous cell carcinoma			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm progression			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	8 / 84 (9.52%)	2 / 57 (3.51%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	8 / 8	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 84 (0.00%)	2 / 57 (3.51%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 0	1 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 84 (1.19%)	1 / 57 (1.75%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 84 (1.19%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 84 (1.19%)	1 / 57 (1.75%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			

subjects affected / exposed	1 / 84 (1.19%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 84 (1.19%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	5 / 84 (5.95%)	9 / 57 (15.79%)	4 / 36 (11.11%)
occurrences causally related to treatment / all	3 / 6	8 / 13	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 84 (1.19%)	1 / 57 (1.75%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 84 (0.00%)	2 / 57 (3.51%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 84 (1.19%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			

subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory distress			
subjects affected / exposed	0 / 84 (0.00%)	2 / 57 (3.51%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 84 (1.19%)	2 / 57 (3.51%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 84 (1.19%)	1 / 57 (1.75%)	4 / 36 (11.11%)
occurrences causally related to treatment / all	1 / 1	1 / 1	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	3 / 36 (8.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	2 / 84 (2.38%)	4 / 57 (7.02%)	3 / 36 (8.33%)
occurrences causally related to treatment / all	2 / 2	4 / 4	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			

subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Incisional hernia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiopulmonary failure			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Encephalopathy			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paresis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 84 (0.00%)	3 / 57 (5.26%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic thrombosis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal dystrophy			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovesical fistula			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal pain			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal toxicity			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			

subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 84 (1.19%)	3 / 57 (5.26%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic duct stenosis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vomiting			
subjects affected / exposed	1 / 84 (1.19%)	2 / 57 (3.51%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular injury			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Blister			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal artery thrombosis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 84 (0.00%)	2 / 57 (3.51%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 84 (0.00%)	2 / 57 (3.51%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 84 (1.19%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	0 / 84 (0.00%)	2 / 57 (3.51%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Furuncle			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Legionella infection			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung infection			
subjects affected / exposed	0 / 84 (0.00%)	2 / 57 (3.51%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia			
subjects affected / exposed	2 / 84 (2.38%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	2 / 84 (2.38%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 84 (1.19%)	2 / 57 (3.51%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed	0 / 84 (0.00%)	2 / 57 (3.51%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 84 (1.19%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Monotherapy All Treated	Combination Second-Line Plus	Combination First-Line
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 84 (97.62%)	54 / 57 (94.74%)	36 / 36 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	5 / 84 (5.95%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences (all)	5	0	0
Basal cell carcinoma			
subjects affected / exposed	2 / 84 (2.38%)	2 / 57 (3.51%)	2 / 36 (5.56%)
occurrences (all)	2	2	2
Keratoacanthoma			

subjects affected / exposed	6 / 84 (7.14%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences (all)	6	0	0
Melanocytic naevus			
subjects affected / exposed	9 / 84 (10.71%)	2 / 57 (3.51%)	0 / 36 (0.00%)
occurrences (all)	12	3	0
Papilloma			
subjects affected / exposed	6 / 84 (7.14%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences (all)	6	0	0
Seborrhoeic keratosis			
subjects affected / exposed	9 / 84 (10.71%)	1 / 57 (1.75%)	1 / 36 (2.78%)
occurrences (all)	11	1	1
Skin papilloma			
subjects affected / exposed	23 / 84 (27.38%)	2 / 57 (3.51%)	0 / 36 (0.00%)
occurrences (all)	40	2	0
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 84 (4.76%)	5 / 57 (8.77%)	2 / 36 (5.56%)
occurrences (all)	4	6	2
Hypotension			
subjects affected / exposed	6 / 84 (7.14%)	6 / 57 (10.53%)	5 / 36 (13.89%)
occurrences (all)	6	7	5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	25 / 84 (29.76%)	19 / 57 (33.33%)	3 / 36 (8.33%)
occurrences (all)	31	23	4
Chest pain			
subjects affected / exposed	7 / 84 (8.33%)	9 / 57 (15.79%)	1 / 36 (2.78%)
occurrences (all)	8	10	1
Chills			
subjects affected / exposed	12 / 84 (14.29%)	13 / 57 (22.81%)	9 / 36 (25.00%)
occurrences (all)	16	18	14
Fatigue			
subjects affected / exposed	23 / 84 (27.38%)	9 / 57 (15.79%)	11 / 36 (30.56%)
occurrences (all)	24	14	11
Hyperthermia			

subjects affected / exposed	0 / 84 (0.00%)	3 / 57 (5.26%)	1 / 36 (2.78%)
occurrences (all)	0	3	1
Influenza like illness			
subjects affected / exposed	2 / 84 (2.38%)	4 / 57 (7.02%)	3 / 36 (8.33%)
occurrences (all)	2	6	6
Malaise			
subjects affected / exposed	5 / 84 (5.95%)	3 / 57 (5.26%)	3 / 36 (8.33%)
occurrences (all)	5	4	4
Mucosal inflammation			
subjects affected / exposed	5 / 84 (5.95%)	4 / 57 (7.02%)	2 / 36 (5.56%)
occurrences (all)	6	5	2
Oedema peripheral			
subjects affected / exposed	3 / 84 (3.57%)	20 / 57 (35.09%)	12 / 36 (33.33%)
occurrences (all)	7	27	14
Pain			
subjects affected / exposed	1 / 84 (1.19%)	1 / 57 (1.75%)	3 / 36 (8.33%)
occurrences (all)	1	1	3
Pyrexia			
subjects affected / exposed	30 / 84 (35.71%)	24 / 57 (42.11%)	22 / 36 (61.11%)
occurrences (all)	47	83	62
Xerosis			
subjects affected / exposed	7 / 84 (8.33%)	4 / 57 (7.02%)	0 / 36 (0.00%)
occurrences (all)	7	4	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 84 (30.95%)	14 / 57 (24.56%)	6 / 36 (16.67%)
occurrences (all)	35	14	6
Dysphonia			
subjects affected / exposed	8 / 84 (9.52%)	2 / 57 (3.51%)	2 / 36 (5.56%)
occurrences (all)	8	2	2
Dyspnoea			
subjects affected / exposed	16 / 84 (19.05%)	12 / 57 (21.05%)	5 / 36 (13.89%)
occurrences (all)	18	16	6
Epistaxis			

subjects affected / exposed	1 / 84 (1.19%)	4 / 57 (7.02%)	1 / 36 (2.78%)
occurrences (all)	1	4	2
Haemoptysis			
subjects affected / exposed	7 / 84 (8.33%)	3 / 57 (5.26%)	1 / 36 (2.78%)
occurrences (all)	8	3	1
Nasal congestion			
subjects affected / exposed	3 / 84 (3.57%)	0 / 57 (0.00%)	2 / 36 (5.56%)
occurrences (all)	3	0	2
Oropharyngeal pain			
subjects affected / exposed	2 / 84 (2.38%)	3 / 57 (5.26%)	1 / 36 (2.78%)
occurrences (all)	2	3	1
Productive cough			
subjects affected / exposed	6 / 84 (7.14%)	7 / 57 (12.28%)	0 / 36 (0.00%)
occurrences (all)	6	11	0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 84 (2.38%)	4 / 57 (7.02%)	1 / 36 (2.78%)
occurrences (all)	2	6	1
Depression			
subjects affected / exposed	3 / 84 (3.57%)	3 / 57 (5.26%)	0 / 36 (0.00%)
occurrences (all)	3	3	0
Insomnia			
subjects affected / exposed	6 / 84 (7.14%)	4 / 57 (7.02%)	3 / 36 (8.33%)
occurrences (all)	6	4	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 84 (3.57%)	4 / 57 (7.02%)	2 / 36 (5.56%)
occurrences (all)	3	5	2
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 84 (3.57%)	5 / 57 (8.77%)	2 / 36 (5.56%)
occurrences (all)	3	6	2
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 84 (5.95%)	9 / 57 (15.79%)	1 / 36 (2.78%)
occurrences (all)	5	10	2
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 84 (0.00%)	5 / 57 (8.77%)	1 / 36 (2.78%)
occurrences (all)	0	6	1
Blood creatinine increased			
subjects affected / exposed	3 / 84 (3.57%)	5 / 57 (8.77%)	1 / 36 (2.78%)
occurrences (all)	4	6	2
Lipase increased			
subjects affected / exposed	2 / 84 (2.38%)	3 / 57 (5.26%)	0 / 36 (0.00%)
occurrences (all)	2	4	0
Weight decreased			
subjects affected / exposed	15 / 84 (17.86%)	8 / 57 (14.04%)	4 / 36 (11.11%)
occurrences (all)	16	9	4
Weight increased			
subjects affected / exposed	0 / 84 (0.00%)	8 / 57 (14.04%)	1 / 36 (2.78%)
occurrences (all)	0	9	1
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	2 / 36 (5.56%)
occurrences (all)	0	1	2
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 84 (2.38%)	1 / 57 (1.75%)	2 / 36 (5.56%)
occurrences (all)	4	1	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 84 (8.33%)	7 / 57 (12.28%)	5 / 36 (13.89%)
occurrences (all)	7	8	5
Dysgeusia			
subjects affected / exposed	4 / 84 (4.76%)	6 / 57 (10.53%)	1 / 36 (2.78%)
occurrences (all)	4	8	1
Headache			
subjects affected / exposed	16 / 84 (19.05%)	8 / 57 (14.04%)	7 / 36 (19.44%)
occurrences (all)	18	14	10
Sciatica			
subjects affected / exposed	0 / 84 (0.00%)	3 / 57 (5.26%)	0 / 36 (0.00%)
occurrences (all)	0	3	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	10 / 84 (11.90%)	8 / 57 (14.04%)	4 / 36 (11.11%)
occurrences (all)	11	11	6
Leukopenia			
subjects affected / exposed	4 / 84 (4.76%)	5 / 57 (8.77%)	1 / 36 (2.78%)
occurrences (all)	4	7	1
Lymphopenia			
subjects affected / exposed	6 / 84 (7.14%)	2 / 57 (3.51%)	1 / 36 (2.78%)
occurrences (all)	7	2	3
Neutropenia			
subjects affected / exposed	2 / 84 (2.38%)	11 / 57 (19.30%)	1 / 36 (2.78%)
occurrences (all)	2	23	3
Thrombocytopenia			
subjects affected / exposed	5 / 84 (5.95%)	5 / 57 (8.77%)	0 / 36 (0.00%)
occurrences (all)	5	6	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 84 (0.00%)	5 / 57 (8.77%)	1 / 36 (2.78%)
occurrences (all)	0	9	1
Eye disorders			
Dry eye			
subjects affected / exposed	4 / 84 (4.76%)	6 / 57 (10.53%)	1 / 36 (2.78%)
occurrences (all)	5	7	1
Eye pain			
subjects affected / exposed	1 / 84 (1.19%)	2 / 57 (3.51%)	2 / 36 (5.56%)
occurrences (all)	1	2	2
Periorbital oedema			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Photopsia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 57 (1.75%)	2 / 36 (5.56%)
occurrences (all)	0	1	2
Vision blurred			
subjects affected / exposed	5 / 84 (5.95%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences (all)	5	3	0
Visual acuity reduced			

subjects affected / exposed	3 / 84 (3.57%)	6 / 57 (10.53%)	1 / 36 (2.78%)
occurrences (all)	3	7	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 84 (9.52%)	4 / 57 (7.02%)	3 / 36 (8.33%)
occurrences (all)	10	4	3
Abdominal pain upper			
subjects affected / exposed	3 / 84 (3.57%)	8 / 57 (14.04%)	0 / 36 (0.00%)
occurrences (all)	3	12	0
Constipation			
subjects affected / exposed	9 / 84 (10.71%)	10 / 57 (17.54%)	5 / 36 (13.89%)
occurrences (all)	9	13	5
Diarrhoea			
subjects affected / exposed	17 / 84 (20.24%)	17 / 57 (29.82%)	13 / 36 (36.11%)
occurrences (all)	27	32	19
Dry mouth			
subjects affected / exposed	1 / 84 (1.19%)	3 / 57 (5.26%)	3 / 36 (8.33%)
occurrences (all)	1	4	3
Dyspepsia			
subjects affected / exposed	2 / 84 (2.38%)	5 / 57 (8.77%)	2 / 36 (5.56%)
occurrences (all)	2	5	2
Dysphagia			
subjects affected / exposed	2 / 84 (2.38%)	3 / 57 (5.26%)	0 / 36 (0.00%)
occurrences (all)	2	3	0
Nausea			
subjects affected / exposed	24 / 84 (28.57%)	22 / 57 (38.60%)	19 / 36 (52.78%)
occurrences (all)	32	38	29
Vomiting			
subjects affected / exposed	18 / 84 (21.43%)	22 / 57 (38.60%)	9 / 36 (25.00%)
occurrences (all)	27	59	18
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	10 / 84 (11.90%)	1 / 57 (1.75%)	3 / 36 (8.33%)
occurrences (all)	17	1	3
Alopecia			

subjects affected / exposed	18 / 84 (21.43%)	6 / 57 (10.53%)	2 / 36 (5.56%)
occurrences (all)	18	6	2
Dermal cyst			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Dry skin			
subjects affected / exposed	20 / 84 (23.81%)	19 / 57 (33.33%)	11 / 36 (30.56%)
occurrences (all)	22	22	11
Eczema			
subjects affected / exposed	3 / 84 (3.57%)	3 / 57 (5.26%)	1 / 36 (2.78%)
occurrences (all)	3	5	1
Erythema			
subjects affected / exposed	1 / 84 (1.19%)	5 / 57 (8.77%)	4 / 36 (11.11%)
occurrences (all)	1	6	5
Hair texture abnormal			
subjects affected / exposed	7 / 84 (8.33%)	3 / 57 (5.26%)	0 / 36 (0.00%)
occurrences (all)	7	3	0
Hyperhidrosis			
subjects affected / exposed	3 / 84 (3.57%)	4 / 57 (7.02%)	1 / 36 (2.78%)
occurrences (all)	3	4	1
Hyperkeratosis			
subjects affected / exposed	25 / 84 (29.76%)	6 / 57 (10.53%)	0 / 36 (0.00%)
occurrences (all)	54	6	0
Madarosis			
subjects affected / exposed	5 / 84 (5.95%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences (all)	5	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	19 / 84 (22.62%)	2 / 57 (3.51%)	1 / 36 (2.78%)
occurrences (all)	22	3	1
Papule			
subjects affected / exposed	8 / 84 (9.52%)	1 / 57 (1.75%)	1 / 36 (2.78%)
occurrences (all)	8	1	1
Pruritus			
subjects affected / exposed	12 / 84 (14.29%)	9 / 57 (15.79%)	4 / 36 (11.11%)
occurrences (all)	12	11	5

Pruritus generalised			
subjects affected / exposed	1 / 84 (1.19%)	3 / 57 (5.26%)	1 / 36 (2.78%)
occurrences (all)	1	5	1
Rash			
subjects affected / exposed	15 / 84 (17.86%)	13 / 57 (22.81%)	7 / 36 (19.44%)
occurrences (all)	15	19	7
Rash generalised			
subjects affected / exposed	2 / 84 (2.38%)	4 / 57 (7.02%)	1 / 36 (2.78%)
occurrences (all)	2	4	1
Rash macular			
subjects affected / exposed	0 / 84 (0.00%)	0 / 57 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	3
Rash maculo-papular			
subjects affected / exposed	5 / 84 (5.95%)	0 / 57 (0.00%)	0 / 36 (0.00%)
occurrences (all)	5	0	0
Rash papular			
subjects affected / exposed	6 / 84 (7.14%)	2 / 57 (3.51%)	2 / 36 (5.56%)
occurrences (all)	6	2	3
Skin lesion			
subjects affected / exposed	5 / 84 (5.95%)	2 / 57 (3.51%)	2 / 36 (5.56%)
occurrences (all)	8	2	3
Urticaria			
subjects affected / exposed	2 / 84 (2.38%)	3 / 57 (5.26%)	1 / 36 (2.78%)
occurrences (all)	5	3	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 84 (20.24%)	12 / 57 (21.05%)	3 / 36 (8.33%)
occurrences (all)	26	15	3
Back pain			
subjects affected / exposed	10 / 84 (11.90%)	4 / 57 (7.02%)	5 / 36 (13.89%)
occurrences (all)	11	6	5
Muscle spasms			
subjects affected / exposed	2 / 84 (2.38%)	6 / 57 (10.53%)	3 / 36 (8.33%)
occurrences (all)	2	8	3
Muscular weakness			

subjects affected / exposed	6 / 84 (7.14%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences (all)	7	1	0
Musculoskeletal chest pain			
subjects affected / exposed	4 / 84 (4.76%)	3 / 57 (5.26%)	3 / 36 (8.33%)
occurrences (all)	5	3	3
Musculoskeletal pain			
subjects affected / exposed	5 / 84 (5.95%)	4 / 57 (7.02%)	3 / 36 (8.33%)
occurrences (all)	7	5	3
Myalgia			
subjects affected / exposed	12 / 84 (14.29%)	7 / 57 (12.28%)	4 / 36 (11.11%)
occurrences (all)	15	10	5
Pain in extremity			
subjects affected / exposed	15 / 84 (17.86%)	2 / 57 (3.51%)	3 / 36 (8.33%)
occurrences (all)	17	2	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 84 (7.14%)	6 / 57 (10.53%)	0 / 36 (0.00%)
occurrences (all)	9	10	0
Conjunctivitis			
subjects affected / exposed	2 / 84 (2.38%)	3 / 57 (5.26%)	0 / 36 (0.00%)
occurrences (all)	2	4	0
Folliculitis			
subjects affected / exposed	3 / 84 (3.57%)	4 / 57 (7.02%)	0 / 36 (0.00%)
occurrences (all)	3	4	0
Gastroenteritis			
subjects affected / exposed	2 / 84 (2.38%)	0 / 57 (0.00%)	2 / 36 (5.56%)
occurrences (all)	3	0	2
Nasopharyngitis			
subjects affected / exposed	9 / 84 (10.71%)	7 / 57 (12.28%)	2 / 36 (5.56%)
occurrences (all)	10	9	2
Pneumonia			
subjects affected / exposed	0 / 84 (0.00%)	2 / 57 (3.51%)	3 / 36 (8.33%)
occurrences (all)	0	2	3
Rhinitis			
subjects affected / exposed	5 / 84 (5.95%)	5 / 57 (8.77%)	0 / 36 (0.00%)
occurrences (all)	6	8	0

Upper respiratory tract infection			
subjects affected / exposed	7 / 84 (8.33%)	1 / 57 (1.75%)	0 / 36 (0.00%)
occurrences (all)	7	1	0
Urinary tract infection			
subjects affected / exposed	5 / 84 (5.95%)	4 / 57 (7.02%)	4 / 36 (11.11%)
occurrences (all)	6	5	5
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	24 / 84 (28.57%)	15 / 57 (26.32%)	9 / 36 (25.00%)
occurrences (all)	31	20	10
Dehydration			
subjects affected / exposed	4 / 84 (4.76%)	3 / 57 (5.26%)	2 / 36 (5.56%)
occurrences (all)	4	3	2
Hyperglycaemia			
subjects affected / exposed	7 / 84 (8.33%)	4 / 57 (7.02%)	1 / 36 (2.78%)
occurrences (all)	8	5	1
Hypoalbuminaemia			
subjects affected / exposed	3 / 84 (3.57%)	4 / 57 (7.02%)	1 / 36 (2.78%)
occurrences (all)	5	4	1
Hypokalaemia			
subjects affected / exposed	5 / 84 (5.95%)	4 / 57 (7.02%)	3 / 36 (8.33%)
occurrences (all)	7	4	3
Hypomagnesaemia			
subjects affected / exposed	3 / 84 (3.57%)	1 / 57 (1.75%)	2 / 36 (5.56%)
occurrences (all)	4	1	5
Hyponatraemia			
subjects affected / exposed	3 / 84 (3.57%)	9 / 57 (15.79%)	4 / 36 (11.11%)
occurrences (all)	4	11	6
Hypophosphataemia			
subjects affected / exposed	6 / 84 (7.14%)	4 / 57 (7.02%)	1 / 36 (2.78%)
occurrences (all)	12	4	1

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 onBRAF 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