Clinical trial results:
MEK114267, A Phase III randomized, open-label study comparing GSK1120212 to chemotherapy in subjects with advanced or metastatic BRAF V600E/K mutation-positive melanoma

Summary

EudraCT number	2010-022838-85
Trial protocol	DE SE BE CZ GR NO GB AT IT
Global end of trial date	16 December 2016

Results information

Result version number	v2
This version publication date	15 February 2018
First version publication date	30 November 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	114267

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	Final
Date of interim/final analysis	17 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study is to establish the superiority of GSK1120212 over chemotherapy with respect to progression-free survival for subjects with advanced/metastatic BRAF V600E mutation-positive melanoma without a history of prior brain metastases

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2010
Long term follow-up planned	Yes
Long term follow-up rationale	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	Argentina: 3
Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Germany: 64
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Russian Federation: 19
Country: Number of subjects enrolled	Sweden: 17
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	Ukraine: 14
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	United States: 20

Worldwide total number of subjects	322
EEA total number of subjects	211

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)	251
From 65 to 84 years	70
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This was a randomized open-label, multi-center Phase III study to evaluate the efficacy and safety of single agent trametinib compared with chemotherapy (CT) (dacarbazine or paclitaxel). Participants (par.) were enrolled by 86 sites in 19 countries from December 2010 to July 2011. Results as of 16 December 2016 data-cut have been presented.

Pre-assignment

Screening details:

Participants (par.) were stratified for lactate dehydrogenase and prior CT for advanced or metastatic disease. 1059 par. were screened and 322 were enrolled to receive trametinib (214 par.) or CT (108 par.) until disease progression, death, or withdrawal. Par. randomized to CT were allowed to cross-over to trametinib if disease progressed.

Period 1

Period 1 title	Randomization and Crossover Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Trametinib

Arm description:

Participants with histologically confirmed cutaneous advanced or metastatic melanoma (Stage IIIC or Stage IV), with a BRAF (a human gene encoding for protein called B-Raf, which is involved in a signaling pathway and is important for cell growth) V600 E/K mutation-positive tumor sample as determined via the central BRAF mutation assay, received a Trametinib 2 milligram (mg) tablet once daily until disease progression, death, or withdrawal.

Arm type	Experimental
Investigational medicinal product name	Trametinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a Trametinib 2 mg tablet once daily until disease progression, death, or withdrawal.

Arm title	Chemotherapy

Arm description:

Participants with histologically confirmed cutaneous advanced or metastatic melanoma (Stage IIIC or Stage IV), with a BRAF V600 E/K mutation-positive tumor sample as determined via the central BRAF mutation assay, received an intravenous (IV) dose of Dacarbazine 1000 mg per square meter every 3 weeks or Paclitaxel 175 mg per square meter every 3 weeks at the discretion of the investigator, provided the participant had not received that type of chemotherapy before randomization, until disease progression, death, or withdrawal.

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Participants received an IV dose of Paclitaxel 175 mg per square meter every 3 weeks at the discretion

of the investigator, provided the participant had not received that type of chemotherapy before randomization, until disease progression, death, or withdrawal.

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Participants received an IV dose of Dacarbazine 1000 mg per square meter every 3 weeks at the discretion of the investigator, provided the participant had not received that type of chemotherapy before randomization, until disease progression, death, or withdrawal.

Number of subjects in period 1	Trametinib	Chemotherapy
Started	214	108
Completed	173	77
Not completed	41	31
Physician decision	2	4
Withdrew Consent	12	11
Study closed/ terminated	23	14
Lost to follow-up	4	2

Period 2

Period 2 title	Cross-over Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Cross-over from Chemotherapy to Trametinib

Arm description:

Participants randomized to chemotherapy and who did not receive subsequent anti-cancer therapy after discontinuing chemotherapy were allowed to cross-over to Trametinib and received 2 mg tablet once daily until disease progression, death or withdrawal.

Arm type	Experimental
Investigational medicinal product name	Trametinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a Trametinib 2 mg tablet once daily until disease progression, death, or withdrawal.

Number of subjects in period 2[1]	Cross-over from Chemotherapy to Trametinib
Started	70
Completed	53
Not completed	17
Physician decision	1
Withdrew Consent	4
Study closed/ terminated	11
Lost to follow-up	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 70 of the 108 participants randomized to chemotherapy in randomization period elected to cross-over to Trametinib and were included in cross-over period.

Baseline characteristics

Reporting groups	
Reporting group title	Trametinib
Reporting group description:	
Participants with histologically confirmed cutaneous advanced or metastatic melanoma (Stage IIIC or Stage IV), with a BRAF (a human gene encoding for protein called B-Raf, which is involved in a signaling pathway and is important for cell growth) V600 E/K mutation-positive tumor sample as determined via the central BRAF mutation assay, received a Trametinib 2 milligram (mg) tablet once daily until disease progression, death, or withdrawal.	
Reporting group title	Chemotherapy
Reporting group description:	
Participants with histologically confirmed cutaneous advanced or metastatic melanoma (Stage IIIC or Stage IV), with a BRAF V600 E/K mutation-positive tumor sample as determined via the central BRAF mutation assay, received an intravenous (IV) dose of Dacarbazine 1000 mg per square meter every 3 weeks or Paclitaxel 175 mg per square meter every 3 weeks at the discretion of the investigator, provided the participant had not received that type of chemotherapy before randomization, until disease progression, death, or withdrawal.	

Reporting group values	Trametinib	Chemotherapy	Total
Number of subjects	214	108	322
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54.3	52.8	
standard deviation	± 12.97	± 13.56	-
Gender categorical Units: Subjects			
Female	94	55	149
Male	120	53	173
Race/Ethnicity, Customized Units: Subjects			
White - Arabic/North African Heritage	2	0	2
White - White/Caucasian/European Heritage	212	107	319
White - Mixed Race	0	1	1

End points

End points reporting groups

Reporting group title	Trametinib

Reporting group description:

Participants with histologically confirmed cutaneous advanced or metastatic melanoma (Stage IIIC or Stage IV), with a BRAF (a human gene encoding for protein called B-Raf, which is involved in a signaling pathway and is important for cell growth) V600 E/K mutation-positive tumor sample as determined via the central BRAF mutation assay, received a Trametinib 2 milligram (mg) tablet once daily until disease progression, death, or withdrawal.

Reporting group title	Chemotherapy

Reporting group description:

Participants with histologically confirmed cutaneous advanced or metastatic melanoma (Stage IIIC or Stage IV), with a BRAF V600 E/K mutation-positive tumor sample as determined via the central BRAF mutation assay, received an intravenous (IV) dose of Dacarbazine 1000 mg per square meter every 3 weeks or Paclitaxel 175 mg per square meter every 3 weeks at the discretion of the investigator, provided the participant had not received that type of chemotherapy before randomization, until disease progression, death, or withdrawal.

Reporting group title	Cross-over from Chemotherapy to Trametinib

Reporting group description:

Participants randomized to chemotherapy and who did not receive subsequent anti-cancer therapy after discontinuing chemotherapy were allowed to cross-over to Trametinib and received 2 mg tablet once daily until disease progression, death or withdrawal.

Primary: Progression-free survival in BRAF V600E mutation-positive participants without a history of brain metastases as assessed by the Investigator and Independent Review

End point title	Progression-free survival in BRAF V600E mutation-positive participants without a history of brain metastases as assessed by the Investigator and Independent Review

End point description:

Progression-free survival (PFS) is defined as the time from randomization to the first documented occurrence of disease progression (PD) or death. PFS for investigator-assessed and blinded, independent, central review committee (BRIC)-assessed responses was summarized per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, which is a set of published rules defining when cancer participants improve (respond), stay the same (stabilize), or worsen (progress) during treatment. Disease progression is defined as at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5 millimeters (mm) or the appearance of at least 1 new lesion, or the worsening of non-target lesions significant enough to require study treatment discontinuation. Primary Efficacy Population included all participants with BRAF V600E mutation-positive melanoma without a history of brain metastases.

End point type	Primary

End point timeframe:

Day 1 until the earliest date of disease progression or death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178[1]	95		
Units: Months				
median (confidence interval 95%)				
Investigator-Assessed	4.8 (3.5 to 4.9)	1.4 (1.4 to 2.7)		
Independent Review	4.9 (4.5 to 5.1)	1.6 (1.4 to 2.8)		

Notes:

[1] - Primary Efficacy Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Investigator-Assessed PFS. HR <1 indicates a lower risk with Trametinib compared with CT. HR from a stratified log-rank test was adjusted for prior chemotherapy for advanced or metastatic disease and Baseline lactate dehydrogenase.

Comparison groups	Trametinib v Chemotherapy
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.64

Notes:

[2] - P-value from a stratified log-rank test was adjusted for prior chemotherapy for advanced or metastatic disease and Baseline lactate dehydrogenase.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Independent Review PFS. HR <1 indicates a lower risk with Trametinib compared with CT. HR from a stratified log-rank test was adjusted for prior chemotherapy for advanced or metastatic disease and Baseline lactate dehydrogenase.

Comparison groups	Trametinib v Chemotherapy
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.6

Notes:

[3] - P-value from a stratified log-rank test was adjusted for prior chemotherapy for advanced or metastatic disease and Baseline lactate dehydrogenase.

Secondary: Progression-free survival in all participants

End point title	Progression-free survival in all participants

End point description:

PFS is defined as the time from the date of randomization to the first documented occurrence of PD or death. Investigator-assessed and BRIC-assessed PFS were summarized per RECIST, Version 1.1. PD is defined as at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions, or the worsening of non-target lesions significant enough to require study treatment discontinuation. Intend-To-Treat (ITT) Population included all randomized participants regardless of whether or not treatment was administered.

End point type	Secondary

End point timeframe:

Day 1 until the earliest date of disease progression or death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214[4]	108		
Units: Months				
median (confidence interval 95%)				
Investigator-Assessed	4.9 (4.5 to 5.0)	1.5 (1.4 to 2.8)		
Independent radiologist assessed-Assessed	4.9 (4.6 to 5.0)	1.5 (1.4 to 2.8)		

Notes:

[4] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in BRAF V600E mutation-positive participants without a history of brain metastases and without prior chemotherapy as assessed by the Investigator

End point title	PFS in BRAF V600E mutation-positive participants without a history of brain metastases and without prior chemotherapy as assessed by the Investigator

End point description:

PFS is defined as the time from the date of randomization to the first documented occurrence of PD or death. Investigator-assessed PFS was summarized per RECIST, Version 1.1. PD is defined as at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions, or the worsening of non-target lesions significant enough to require study treatment discontinuation.

End point type	Secondary

End point timeframe:

Day 1 until the earliest date of disease progression or death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114[5]	62		
Units: Months				
median (confidence interval 95%)				
Months	4.8 (3.4 to 5.0)	1.4 (1.4 to 1.7)		

Notes:

[5] - Primary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in BRAF V600E mutation-positive participants without a history of brain metastases and with prior chemotherapy as assessed by the Investigator

End point title	PFS in BRAF V600E mutation-positive participants without a history of brain metastases and with prior chemotherapy as assessed by the Investigator

End point description:

PFS is defined as the time from the date of randomization to the first documented occurrence of PD or death. Investigator-assessed PFS was summarized per RECIST, Version 1.1. PD is defined as at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions, or the worsening of non-target lesions significant enough to require study treatment discontinuation.

End point type	Secondary

End point timeframe:

Day 1 until the earliest date of disease progression or death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[6]	33		
Units: Months				
median (confidence interval 95%)				
Months	4.8 (2.9 to 4.9)	2.7 (1.4 to 2.9)		

Notes:

[6] - Primary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival in all participants

End point title	Overall Survival in all participants

End point description:

Overall survival was defined as the time from the date of randomization to the date of death due to any cause.

End point type	Secondary

End point timeframe:

Day 1 until death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214[7]	108		
Units: Months				
median (confidence interval 95%)				
Months	15.6 (13.5 to 17.3)	11.3 (7.2 to 14.8)		

Notes:

[7] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival in BRAF V600E mutation-positive participants without a history of brain metastases

End point title	Overall Survival in BRAF V600E mutation-positive participants without a history of brain metastases

End point description:

Overall survival was defined as the time from the date of randomization to the date of death due to any cause. 99999 indicates that data were not available.

End point type	Secondary

End point timeframe:

Day 1 until death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178[8]	95		
Units: Months				
median (confidence interval 95%)				
Months	99999 (-99999 to 99999)	99999 (6.8 to 99999)		

Notes:

[8] - Primary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of BRAF V600E mutation-positive participants without a history of brain metastases with Overall Response (OR) as assessed by the Investigator and Independent Review

End point title	Number of BRAF V600E mutation-positive participants without a history of brain metastases with Overall Response (OR) as assessed by the Investigator and Independent Review

End point description:

OR is defined as the number of participants with evidence of complete response (CR; disappearance of all target lesions. Any pathological lymph node must be less than 10 mm in the short axis) or partial response (PR: at least a 30% decrease in the sum of the diameters of target lesions) evaluated by the Investigator and an independent review per RECIST, Version 1.1.

End point type	Secondary

End point timeframe:

Day 1 until the earliest date of disease progression or death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178[9]	95		
Units: Participants				
Investigator-Assessed: CR	4	0		
Investigator-Assessed: PR	39	7		
Independent Review: CR	0	0		
Independent Review: PR	33	3		

Notes:

[9] - Primary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with OR as assessed by the Investigator and Independent Review

End point title	Number of participants with OR as assessed by the Investigator and Independent Review

End point description:

OR is defined as the number of participants with evidence of complete response (disappearance of all target lesions. Any pathological lymph node must be less than 10 mm in the short axis) or partial response (at least a 30% decrease in the sum of the diameters of target lesions) evaluated by the Investigator and an independent review per RECIST, Version 1.1.

End point type	Secondary

End point timeframe:

Day 1 until the earliest date of disease progression or death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214[10]	108		
Units: Participants				
Investigator-Assessed: CR	8	2		
Investigator-Assessed: PR	53	8		
Independent Review: CR	0	1		
Independent Review: PR	41	4		

Notes:

[10] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of BRAF V600E mutation-positive participants classified as confirmed responders (CR and PR) as assessed by the Investigator

End point title	Number of BRAF V600E mutation-positive participants classified as confirmed responders (CR and PR) as assessed by the Investigator

End point description:

OR is defined as the number of participants with evidence of complete response (disappearance of all extranodal lesions. Any pathological lymph node must be less than 10 mm in the short axis) or partial response (at least a 30% decrease in the sum of the diameters of target lesions) evaluated by the Investigator per RECIST, Version 1.1.

End point type	Secondary

End point timeframe:

Day 1 until the earliest date of disease progression or death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184[11]	97		
Units: Participants				
V600E Mutation, CR	4	0		
V600E Mutation, PR	40	7		

Notes:

[11] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of BRAF V600K mutation-positive participants classified as confirmed responders (CR and PR) as assessed by the Investigator

End point title	Number of BRAF V600K mutation-positive participants classified as confirmed responders (CR and PR) as assessed by the Investigator

End point description:

OR is defined as the number of participants with evidence of complete response (CR; disappearance of all extranodal lesions. Any pathological lymph node must be less than 10 mm in the short axis) or partial response (PR: at least a 30% decrease in the sum of the diameters of target lesions) evaluated by the Investigator per RECIST, Version 1.1.

End point type	Secondary

End point timeframe:

Day 1 until the earliest date of disease progression or death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[12]	11		
Units: Participants				
V600K Mutation, CR	0	0		
V600K Mutation, PR	3	2		

Notes:

[12] - ITT Population: only those participants withV600K mutation-positive melanoma were assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with OR following Cross-over to Trametinib

End point title	Number of participants with OR following Cross-over to Trametinib

End point description:

OR is defined as the number of participants with evidence of CR (disappearance of all target lesions. Any pathological lymph node must be less than 10 millimeters in the short axis) or PR (at least a 30% decrease in the sum of the diameters of target lesions) evaluated by the Investigator in participants following cross-over to Trametinib. The evaluation was carried out by the Investigator per RECIST, Version 1.1. Cross-over Population included the subset of participants who were randomized to CT and who elected to cross-over to Trametinib following disease progression on CT. Only participants who received at least one dose of Trametinib were included in this population.

End point type	Secondary

End point timeframe:

Day 1 of cross-over therapy until the earliest date of disease progression or death due to any cause (average of 18.3 months)

End point values	Cross-over from Chemotherapy to Trametinib			
Subject group type	Reporting group			
Number of subjects analysed	70[13]			
Units: Participants				
CR	2			
PR	29			

Notes:

[13] - Cross-over Population

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) for all BRAF V600E mutation-positive participants without a prior history of brain metastases classified as confirmed responders (CR or PR) as assessed by the Investigator Review

End point title	Duration of Response (DoR) for all BRAF V600E mutation-positive participants without a prior history of brain metastases classified as confirmed responders (CR or PR) as assessed by the Investigator Review

End point description:

DoR is defined as the time from the first documented evidence of CR (disappearance of all target lesions. Any pathological lymph node must be less than 10 mm in the short axis) or PR (at least a 30% decrease in the sum of the diameters of target lesions) until PD (at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions, or the worsening of non-target lesions significant enough to require study treatment discontinuation) or death due to any cause. DoR for the investigator-assessed (INVA) response data were summarized per RECIST, Version 1.1. Only those participants with confirmed response (CR and PR) were analyzed. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles). 99999 indicates that data were not available.

End point type	Secondary

End point timeframe:

Day 1 until the earliest date of disease progression or death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43[14]	7		
Units: Months				
median (confidence interval 95%)				
Months	5.5 (4.9 to 5.9)	99999 (3.5 to 99999)		

Notes:

[14] - Primary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: DoR for all BRAF V600E mutation-positive participants without a prior history of brain metastases classifed as confirmed responders (CR or PR) as assessed by the Independent Review

End point title	DoR for all BRAF V600E mutation-positive participants without a prior history of brain metastases classifed as confirmed responders (CR or PR) as assessed by the Independent Review

End point description:

DoR is defined as the time from the first documented evidence of CR (disappearance of all target lesions. Any pathological lymph node must be less than 10 mm in the short axis) or PR (at least a 30% decrease in the sum of the diameters of target lesions) until PD (at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions, or the worsening of non-target lesions significant enough to require study treatment discontinuation) or death due to any cause. DoR for the independently-assessed (INDA) response data were summarized per RECIST, Version 1.1. Only those participants with confirmed response (CR and PR) were analyzed. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles). 99999 indicates data was not available.

End point type	Secondary

End point timeframe:

Day 1 until the earliest date of disease progression or death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[15]	3		
Units: Months				
median (confidence interval 95%)	5.6 (3.8 to 5.9)	99999 (3.5 to 99999)		

Notes:

[15] - Primary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: DoR for all confirmed responders (CR or PR) as assessed by the Investigator Review

End point title	DoR for all confirmed responders (CR or PR) as assessed by the Investigator Review

End point description:

DoR is defined as the time from the first documented evidence of CR (disappearance of all target lesions. Any pathological lymph node must be less than 10 mm in the short axis) or PR (at least a 30% decrease in the sum of the diameters of target lesions) until PD or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions, or the worsening of non-target lesions significant enough to require study treatment discontinuation. DoR for the INVA response data was summarized per RECIST, Version 1.1. Only those participants with confirmed response (CR and PR) were analyzed. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles). 99999 indicates that data were not available.

End point type	Secondary

End point timeframe:

Day 1 until the earliest date of disease progression or death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[16]	9		
Units: Months				
median (confidence interval 95%)				
Months	5.5 (4.1 to 5.9)	99999 (5.0 to 99999)		

Notes:

[16] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: DoR for all confirmed responders (CR or PR) as assessed by the Independent Review

End point title	DoR for all confirmed responders (CR or PR) as assessed by the Independent Review

End point description:

DoR is defined as thetime from the first documented evidence of CR (disappearance of all target

lesions. Any pathological lymph node must be less than 10 mm in the short axis) or PR (at least a 30% decrease in the sum of the diameters of target lesions) until PD or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions, or the worsening of non-target lesions significant enough to require study treatment discontinuation. DoR for the INDA response data was summarized per RECIST, Version 1.1. Only those participants with confirmed response (CR and PR) were analyzed. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles). 99999 indicates data was not available.

End point type	Secondary

End point timeframe:

Day 1 until the earliest date of disease progression or death due to any cause (average of 20.3 months)

End point values	Trametinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[17]	5		
Units: Months				
median (confidence interval 95%)	5.6 (4.1 to 5.9)	99999 (3.5 to 99999)		

Notes:

[17] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: DoR for all responders (CR or PR) following cross-over to Trametinib as assessed by the Investigator

End point title	DoR for all responders (CR or PR) following cross-over to Trametinib as assessed by the Investigator

End point description:

DoR is defined as the time from the first documented evidence of CR (disappearance of all extra nodal lesions. Any pathological lymph node must be less than 10 mm in the short axis) or PR (at least a 30% decrease in the sum of the diameters of target lesions) until PD or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions, or the worsening of non-target lesions significant enough to require study treatment discontinuation. DoR data were summarized per RECIST, Version 1.1Only those participants with confirmed response (CR and PR) were analyzed. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles). 99999 indicates that data were not available.

End point type	Secondary

End point timeframe:

Day 1 of cross-over therapy until the earliest date of disease progression or death due to any cause (average of 18.3 months)

End point values	Cross-over from Chemotherapy to Trametinib			
Subject group type	Reporting group			
Number of subjects analysed	70[18]			
Units: Months				

median (confidence interval 95%)				
Months	2.7 (1.3 to 99999)			

Notes:

[18] - Cross-over Population

Statistical analyses

No statistical analyses for this end point

Secondary: PFS following cross-over to Trametinib as assessed by the Investigator

End point title	PFS following cross-over to Trametinib as assessed by the Investigator

End point description:

PFS is defined as the time from the first dose of cross-over therapy to the first documented occurrence of PD or death. PFS was summarized per RECIST, Version 1.1. PD is defined as at least a 20% increase in the sum of the diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions, or the worsening of non-target lesions significant enough to require study treatment discontinuation.

End point type	Secondary

End point timeframe:

Day 1 of cross-over therapy until the earliest date of disease progression or death due to any cause (average of 18.3 months)

End point values	Cross-over from Chemotherapy to Trametinib			
Subject group type	Reporting group			
Number of subjects analysed	70[19]			
Units: Months				
median (confidence interval 95%)				
Months	3.0 (2.7 to 4.8)			

Notes:

[19] - Cross-over Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants were analyzed from the first dose of study medication to 28 days after discontinuation of study medication (average of 20.3 months in the Randomization Phase and 18.3 months in the Cross-over Phase).

Adverse event reporting additional description:

Serious adverse events (SAEs) and non-serious AEs were collected in the Safety Population, comprised of all randomized participants included in the study who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Trametinib

Reporting group description:

Participants with histologically confirmed cutaneous advanced or metastatic melanoma (Stage IIIC or Stage IV), with a BRAF (a human gene encoding for protein called B-Raf, which is involved in a signaling pathway and is important for cell growth) V600 E/K mutation-positive tumor sample as determined via the central BRAF mutation assay, received a Trametinib 2 milligram (mg) tablet once daily until disease progression, death, or withdrawal.

Reporting group title	Cross-over from Chemotherapy to Trametinib

Reporting group description:

Participants randomized to chemotherapy and who did not receive subsequent anti-cancer therapy after discontinuing chemotherapy were allowed to cross-over to Trametinib and received 2 mg tablet once daily until disease progression, death or withdrawal.

Reporting group title	Chemotherapy

Reporting group description:

Participants with histologically confirmed cutaneous advanced or metastatic melanoma (Stage IIIC or Stage IV), with a BRAF V600 E/K mutation-positive tumor sample as determined via the central BRAF mutation assay, received an intravenous (IV) dose of Dacarbazine 1000 mg per square meter every 3 weeks or Paclitaxel 175 mg per square meter every 3 weeks at the discretion of the investigator, provided the participant had not received that type of chemotherapy before randomization, until disease progression, death, or withdrawal.

Serious adverse events	Trametinib	Cross-over from Chemotherapy to Trametinib	Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 211 (24.64%)	18 / 70 (25.71%)	19 / 99 (19.19%)
number of deaths (all causes)	172	53	22
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 211 (0.95%)	1 / 70 (1.43%)	0 / 99 (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

Rectal cancer			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Prostate cancer			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Orthostatic hypotension			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Haematoma			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Hypertensive crisis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Lymphoedema			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
General disorders and administration site conditions			
Axillary pain			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Edema			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
General physical health deterioration			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Pain			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 211 (1.42%)	2 / 70 (2.86%)	4 / 99 (4.04%)
occurrences causally related to treatment / all	1 / 3	0 / 2	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal graft rejection			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Hypersensitivity			

subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	3 / 211 (1.42%)	0 / 70 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	2 / 211 (0.95%)	0 / 70 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 211 (0.95%)	0 / 70 (0.00%)	0 / 99 (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
Pneumonitis			
subjects affected / exposed	4 / 211 (1.90%)	1 / 70 (1.43%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	4 / 6	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 211 (1.42%)	1 / 70 (1.43%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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

Pneumothorax			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Hallucination			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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	2 / 211 (0.95%)	0 / 70 (0.00%)	0 / 99 (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
Blood albumin decreased			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Ejection fraction decreased			
subjects affected / exposed	2 / 211 (0.95%)	0 / 70 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hemoglobin decreased			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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			
Acute coronary syndrome			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Conduction disorder			

subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Left ventricular dysfunction			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Myocardial infarction			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Ischemic stroke			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Syncope			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Carotid artery dissection			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Headache			

subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Migraine			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Aphasia			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 211 (1.42%)	1 / 70 (1.43%)	2 / 99 (2.02%)
occurrences causally related to treatment / all	1 / 3	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eyelid ptosis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Retinal vein occlusion			
subjects affected / exposed	2 / 211 (0.95%)	0 / 70 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhea			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric hemorrhage			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Nausea			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 211 (1.42%)	1 / 70 (1.43%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 3	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Gastritis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Gastritis erosive			

subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Large intestinal ulcer			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder obstruction			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Hepatic failure			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 211 (0.95%)	0 / 70 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	2 / 211 (0.95%)	0 / 70 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Urinary retention			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Rhabdomyolysis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Arthralgia			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Myopathy			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cellulitis			
subjects affected / exposed	4 / 211 (1.90%)	2 / 70 (2.86%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 6	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	5 / 211 (2.37%)	1 / 70 (1.43%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye infection			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Infection			
subjects affected / exposed	2 / 211 (0.95%)	0 / 70 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella infection			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Localized infection			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Lymphangitis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Pneumonia			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Rash pustular			

subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Sepsis			
subjects affected / exposed	1 / 211 (0.47%)	1 / 70 (1.43%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Endocarditis			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Lower respiratory tract infection			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Wound infection staphylococcal			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Arthritis bacterial			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Device related infection			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Infected seroma			

subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Infected skin ulcer			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Respiratory tract infection			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Skin infection			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Streptococcal sepsis			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Urosepsis			
subjects affected / exposed	0 / 211 (0.00%)	1 / 70 (1.43%)	0 / 99 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	0 / 99 (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
Dehydration			

subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
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	Trametinib	Cross-over from Chemotherapy to Trametinib	Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	207 / 211 (98.10%)	66 / 70 (94.29%)	88 / 99 (88.89%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	16 / 211 (7.58%)	0 / 70 (0.00%)	3 / 99 (3.03%)
occurrences (all)	22	0	3
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 211 (9.95%)	7 / 70 (10.00%)	1 / 99 (1.01%)
occurrences (all)	29	14	1
Blood alkaline phosphatase increased			
subjects affected / exposed	13 / 211 (6.16%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences (all)	15	0	1
Neutrophil count decreased			
subjects affected / exposed	2 / 211 (0.95%)	0 / 70 (0.00%)	5 / 99 (5.05%)
occurrences (all)	17	0	7
Platelet count decreased			
subjects affected / exposed	1 / 211 (0.47%)	0 / 70 (0.00%)	5 / 99 (5.05%)
occurrences (all)	2	0	6
Weight decreased			
subjects affected / exposed	0 / 211 (0.00%)	4 / 70 (5.71%)	0 / 99 (0.00%)
occurrences (all)	0	4	0
Vascular disorders			
Hypertension			
subjects affected / exposed	40 / 211 (18.96%)	9 / 70 (12.86%)	9 / 99 (9.09%)
occurrences (all)	54	11	9
Lymphedema			

subjects affected / exposed	18 / 211 (8.53%)	6 / 70 (8.57%)	0 / 99 (0.00%)
occurrences (all)	18	9	0
Nervous system disorders			
Headache			
subjects affected / exposed	30 / 211 (14.22%)	0 / 70 (0.00%)	15 / 99 (15.15%)
occurrences (all)	40	0	16
Paraesthesia			
subjects affected / exposed	10 / 211 (4.74%)	0 / 70 (0.00%)	9 / 99 (9.09%)
occurrences (all)	11	0	10
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 211 (1.42%)	0 / 70 (0.00%)	9 / 99 (9.09%)
occurrences (all)	3	0	13
Dysgeusia			
subjects affected / exposed	12 / 211 (5.69%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences (all)	14	0	1
Dizziness			
subjects affected / exposed	0 / 211 (0.00%)	7 / 70 (10.00%)	0 / 99 (0.00%)
occurrences (all)	0	7	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 211 (5.69%)	4 / 70 (5.71%)	12 / 99 (12.12%)
occurrences (all)	13	5	14
Fatigue			
subjects affected / exposed	62 / 211 (29.38%)	8 / 70 (11.43%)	29 / 99 (29.29%)
occurrences (all)	79	9	37
Mucosal inflammation			
subjects affected / exposed	15 / 211 (7.11%)	6 / 70 (8.57%)	0 / 99 (0.00%)
occurrences (all)	23	8	0
Pyrexia			
subjects affected / exposed	15 / 211 (7.11%)	6 / 70 (8.57%)	8 / 99 (8.08%)
occurrences (all)	20	6	9
Oedema peripheral			
subjects affected / exposed	55 / 211 (26.07%)	16 / 70 (22.86%)	2 / 99 (2.02%)
occurrences (all)	76	22	2
Inflammation			

subjects affected / exposed	0 / 211 (0.00%)	4 / 70 (5.71%)	0 / 99 (0.00%)
occurrences (all)	0	4	0
Influenza like illness			
subjects affected / exposed	0 / 211 (0.00%)	4 / 70 (5.71%)	0 / 99 (0.00%)
occurrences (all)	0	8	0
Peripheral swelling			
subjects affected / exposed	0 / 211 (0.00%)	4 / 70 (5.71%)	0 / 99 (0.00%)
occurrences (all)	0	6	0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	13 / 211 (6.16%)	0 / 70 (0.00%)	10 / 99 (10.10%)
occurrences (all)	17	0	11
Neutropenia			
subjects affected / exposed	5 / 211 (2.37%)	0 / 70 (0.00%)	6 / 99 (6.06%)
occurrences (all)	12	0	10
Thrombocytopenia			
subjects affected / exposed	2 / 211 (0.95%)	0 / 70 (0.00%)	5 / 99 (5.05%)
occurrences (all)	2	0	7
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	19 / 211 (9.00%)	0 / 70 (0.00%)	2 / 99 (2.02%)
occurrences (all)	25	0	2
Abdominal pain upper			
subjects affected / exposed	16 / 211 (7.58%)	4 / 70 (5.71%)	3 / 99 (3.03%)
occurrences (all)	23	5	3
Constipation			
subjects affected / exposed	34 / 211 (16.11%)	12 / 70 (17.14%)	22 / 99 (22.22%)
occurrences (all)	40	0	25
Diarrhea			
subjects affected / exposed	94 / 211 (44.55%)	24 / 70 (34.29%)	16 / 99 (16.16%)
occurrences (all)	161	35	29
Dry mouth			
subjects affected / exposed	19 / 211 (9.00%)	6 / 70 (8.57%)	2 / 99 (2.02%)
occurrences (all)	21	6	2
Nausea			

subjects affected / exposed	48 / 211 (22.75%)	12 / 70 (17.14%)	39 / 99 (39.39%)
occurrences (all)	64	14	55
Stomatitis			
subjects affected / exposed	13 / 211 (6.16%)	0 / 70 (0.00%)	1 / 99 (1.01%)
occurrences (all)	20	0	1
Vomiting			
subjects affected / exposed	33 / 211 (15.64%)	16 / 70 (22.86%)	21 / 99 (21.21%)
occurrences (all)	38	23	23
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 211 (11.37%)	4 / 70 (5.71%)	6 / 99 (6.06%)
occurrences (all)	29	6	6
Dyspnea			
subjects affected / exposed	15 / 211 (7.11%)	4 / 70 (5.71%)	6 / 99 (6.06%)
occurrences (all)	16	5	6
Epistaxis			
subjects affected / exposed	15 / 211 (7.11%)	4 / 70 (5.71%)	1 / 99 (1.01%)
occurrences (all)	22	5	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	38 / 211 (18.01%)	7 / 70 (10.00%)	19 / 99 (19.19%)
occurrences (all)	38	7	19
Dermatitis acneiform			
subjects affected / exposed	42 / 211 (19.91%)	10 / 70 (14.29%)	2 / 99 (2.02%)
occurrences (all)	46	15	2
Dry skin			
subjects affected / exposed	30 / 211 (14.22%)	10 / 70 (14.29%)	1 / 99 (1.01%)
occurrences (all)	33	11	1
Eczema			
subjects affected / exposed	12 / 211 (5.69%)	6 / 70 (8.57%)	0 / 99 (0.00%)
occurrences (all)	13	6	0
Pruritus			
subjects affected / exposed	25 / 211 (11.85%)	10 / 70 (14.29%)	1 / 99 (1.01%)
occurrences (all)	31	10	1
Rash			

subjects affected / exposed	123 / 211 (58.29%)	37 / 70 (52.86%)	10 / 99 (10.10%)
occurrences (all)	183	51	12
Hyperhidrosis			
subjects affected / exposed	0 / 211 (0.00%)	0 / 70 (0.00%)	6 / 99 (6.06%)
occurrences (all)	0	0	6
Skin fissures			
subjects affected / exposed	21 / 211 (9.95%)	9 / 70 (12.86%)	0 / 99 (0.00%)
occurrences (all)	28	43	0
Rash macular			
subjects affected / exposed	0 / 211 (0.00%)	5 / 70 (7.14%)	0 / 99 (0.00%)
occurrences (all)	0	7	0
Rash maculo-papular			
subjects affected / exposed	0 / 211 (0.00%)	4 / 70 (5.71%)	0 / 99 (0.00%)
occurrences (all)	0	9	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 211 (7.11%)	4 / 70 (5.71%)	7 / 99 (7.07%)
occurrences (all)	16	4	7
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 211 (9.00%)	0 / 70 (0.00%)	10 / 99 (10.10%)
occurrences (all)	25	0	13
Back pain			
subjects affected / exposed	18 / 211 (8.53%)	0 / 70 (0.00%)	9 / 99 (9.09%)
occurrences (all)	23	0	10
Myalgia			
subjects affected / exposed	3 / 211 (1.42%)	0 / 70 (0.00%)	6 / 99 (6.06%)
occurrences (all)	3	0	11
Pain in extremity			
subjects affected / exposed	13 / 211 (6.16%)	4 / 70 (5.71%)	8 / 99 (8.08%)
occurrences (all)	14	9	9
Infections and infestations			
Folliculitis			
subjects affected / exposed	22 / 211 (10.43%)	6 / 70 (8.57%)	2 / 99 (2.02%)
occurrences (all)	26	7	2
Paronychia			

subjects affected / exposed	26 / 211 (12.32%)	10 / 70 (14.29%)	1 / 99 (1.01%)
occurrences (all)	37	34	1
Nasopharyngitis			
subjects affected / exposed	15 / 211 (7.11%)	0 / 70 (0.00%)	4 / 99 (4.04%)
occurrences (all)	17	0	7
Rash pustular			
subjects affected / exposed	11 / 211 (5.21%)	5 / 70 (7.14%)	0 / 99 (0.00%)
occurrences (all)	15	6	0
Cellulitis			
subjects affected / exposed	0 / 211 (0.00%)	4 / 70 (5.71%)	0 / 99 (0.00%)
occurrences (all)	0	8	0
Nail infection			
subjects affected / exposed	0 / 211 (0.00%)	4 / 70 (5.71%)	0 / 99 (0.00%)
occurrences (all)	0	7	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	18 / 211 (8.53%)	6 / 70 (8.57%)	10 / 99 (10.10%)
occurrences (all)	23	6	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2010	Amendment 01: 1. Corrected the European Clinical Trials Database (Eudra-CT) number. 2. Changed primary endpoint to progression free survival and added crossover to GSK1120212 after progression on the chemotherapy arm based on feedback from the European Medicines Agency (EMEA). 3. After considering the standard of ophthalmological practice across different countries and after consultation with GlaxoSmithKline (GSK) ophthalmologist, GSK recommends the following changes to the ophthalmological guidelines: - Removal of perimetry from ophthalmologic exclusion criteria. Assessment of visual field defects can be done either by automated or confrontational method as per the local standard of care. - Changed requirement for color fundus photos and retinal specialist consultation such that they are recommended if available, but not mandated. Fundus photos were meant to help diagnose any changes to the retina, however adequate documentation of baseline fundus exam would also provide the same information and is the standard ophthalmological practice in a number of countries. - In par. with clinical suspicion of Retinal vein occlusion (RVO) or Central serous retinopathy (CSR), it is recommended that diagnostic studies be completed that are the standard of care in that particular country and may include color fundus photos, fluorescein angiography and/or optical coherence tomography. The studies could be done by an experienced general ophthalmologist or by a retinal specialist. 4. Changed Inclusion Criteria to allow prior treatment with ipilumimab in the adjuvant setting to expand participant population. 5. Changed exclusion to allow par. with prior brain metastases that meet specific criteria to expand participant population. 6. Removed Day 1 Cycle 3 blank column from Time and Events Table and updated several footnotes based on above changes.7. Added crossover study extension Time and Events table 8. Corrected minor administrative and typographical errors.
02 May 2011	Amendment 02: Updated contact information. Changed eligibility criteria (EC) to indicate that par. having received one prior chemotherapy regimen in the advanced/metastatic setting must have had documented progression prior to randomization. Clarified EC to allow use of low molecular weight heparin; par. with second malignancies that are indolent or definitively treated to indicate that they must be disease free for at least 3 years; par. with brain metastases to indicate that prior whole brain radiotherapy is not allowed and confirmation of stable and/or no evidence of disease is required prior to randomization; cardiac history to indicate that the time frame of '6 months prior to randomization' applies to all conditions listed in that criterion. Updated crossover eligibility to allow par. who discontinue from chemotherapy arm of the study for a reason other than disease progression, but who do not receive any further anticancer treatment and eventually have documented disease progression to be eligible for crossover to GSK1120212. Clarified dosing instructions and related process. Corrected laboratory values in dose modification instructions for chemotherapy treatment arm. Clarified requirements for submission or Echocardiogram/ Multi-gated acquisition scan (ECHO/MUGA) to the central imaging vendor. Added concomitant palliative radiotherapy to Prohibited Medications Section. Removed allowance for sending tissue for BRAF mutation testing up to 6 months prior to randomization. Changed direct fundoscopy to an optional assessment within the required ophthalmic examination at screening. Changed required duration of adequate contraception usage by women of childbearing potential to 16 weeks after discontinuation of study medication. Changed tumor tissue requirements for BRAF mutation testing to indicate that tissue from the current state of disease is preferred, but tissue from primary site is also acceptable. Corrected minor administrative and typographical errors.

03 October 2011	Amendment 03: Data from the Phase II study (MEK113583) study with GSK1120212 in V600 mutation positive melanoma par. previously treated with chemotherapy and/or immunotherapy were presented by Dr. Lewis (University of Colorado) at Perspectives in Melanoma meeting on September 16, 2011. These phase 2 data confirm that the 2 mg QD dose of GSK1120212 is well tolerated, has clinical activity in previously treated BRAF-mutant metastatic melanoma par., and suggest that the subset of V600E mutation-positive par. with no history of prior brain metastases has a better median PFS compared to the overall study population. Rationale for Change: Due to these phase II data, the population for the primary analysis of MEK114267 is being changed to only those par. with a BRAF V600E mutational status without a history of prior brain metastases. This change will ensure that the study focuses on the population most likely to benefit from GSK1120212. As it is still important to understand the effect of GSK1120212 in par. with BRAF V600K mutations, the secondary endpoints evaluating this population remain. Due to the limited number of par. with a prior history of brain metastases, secondary endpoints evaluating this population are not planned; however analyses including and excluding par. with a prior history of brain metastases will be explored This change to the primary endpoint is being made prior to Data Base Freeze to conduct the primary endpoint analysis of progression free survival.
27 January 2012	Amendment 04: Dear Investigator Letter was issued 09 January 2012 which stated that emerging data suggests that par. treated with GSK1120212 may develop hypertension or have worsening control of pre-existing hypertension. As a result, hypertension monitoring and management guidelines are being incorporated into all ongoing studies with GSK1120212.
16 February 2012	Amendment 05: The planned primary analysis was completed on 27 January 2012 and reviewed by the Independent Data Monitoring Committee (IDMC) that comprised medical oncology experts and a statistician. The IDMC unanimously recommended to allow immediate crossover of any par. enrolled and treated on the chemotherapy arm to GSK1120212 (trametinib). This recommendation is based upon a clinically meaningful, statistically significant improvement in the primary endpoint of progression free survival (PFS) in the trametinib arm versus chemotherapy arm. The safety profile of GSK1120212 is consistent to what has been observed in prior studies.
10 September 2012	Amendment 06: There is a change from the older Parma supplies (white 0.5 mg tablets) with product codes BQ (0.5 mg), BR (1 mg), BS (2 mg) to the newer Parma supplies with commercial image (non-debossed) tablets with product codes CL/CT (0.5 mg), CM/CS (2 mg) product codes for upcoming resupplies. The investigational product description must be updated to properly describe the new supply.
16 January 2014	Amendment 07: 1. Updated study objectives to include secondary efficacy objective of long-term overall survival. 2. Updated definition of study completion throughout to allow for collection of long-term survival data. 3. Removed option to transition to rollover study after study completion. 4. Updated withholding criteria for visual changes. 5. Updated QTc stopping criteria. 6. Updated visit schedule. 7. Minor administrative changes and typographical corrections throughout.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported