Clinical trial results:
The NEMO trial (NRAS melanoma and MEK inhibitor): A randomized Phase III, open label, multicenter, two-arm study comparing MEK162 versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma

Summary

EudraCT number	2012-003593-51
Trial protocol	SK AT CZ DE ES GB NL BE IT HU GR SE PL PT FR
Global end of trial date	04 June 2019

Results information

Result version number	v1 (current)
This version publication date	10 May 2020
First version publication date	10 May 2020

Trial information

Trial identification

Sponsor protocol code	CMEK162A2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01763164
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Array BioPharma Inc.
Sponsor organisation address	3200 Walnut Street, Boulder, Colorado, United States, 80301
Public contact	Abdu Nessralla, Array BioPharma Inc., +1 857 600 3719, abdu.nessralla@arraybiopharma.com
Scientific contact	Abdu Nessralla, Array BioPharma Inc., +1 857 600 3719, abdu.nessralla@arraybiopharma.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 June 2019
Global end of trial reached?	Yes
Global end of trial date	04 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether treatment with MEK162 prolongs PFS as compared to dacarbazine in patients with advanced unresectable, or metastatic NRAS mutation-positive cutaneous or unknown primary melanoma who are previously untreated or who have progressed on or after prior treatment with any number of lines of immunotherapy for unresectable or metastatic disease.

Protection of trial subjects:

The study was conducted according to the ethical principles of the Declaration of Helsinki.
Informed consent was obtained from each patient in writing before randomization. The study was described by the Investigator, who answered any questions, and written information was also provided. The patient first gave consent for a neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS) mutation status test at a central laboratory designated by Novartis by signing the molecular prescreening informed consent form (ICF).
Patients were also asked to participate in the optional biomarker sampling. A separate biomarker ICF was provided.

Background therapy:

Patients taking concomitant medications chronically maintained the same dose and dose schedule throughout the study as medically feasible. On the days PK blood sampling was performed, the patient continued their consistent use of other concomitant medication. Intermittently concomitant therapy use during the study was avoided on PK days. All concomitant medications and/or therapies were recorded in the patient's source documents and eCRFs. Concomitant medications of specific interest were summarized separately.

Evidence for comparator:

Dacarbazine (or locally approved generics) - patients randomized to dacarbazine received an IV infusion of dacarbazine 1000 mg/m2 over the course of 1 hour on day 1 and then every three weeks.

Actual start date of recruitment	30 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Austria: 11

Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	Germany: 89
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Italy: 58
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	Switzerland: 15
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	402
EEA total number of subjects	307

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)	210
From 65 to 84 years	192
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 402 patients were randomized 2:1 to receive either MEK162 or dacarbazine. Patients were stratified according to AJCC stage (IIIC, IVM1a, and IVM1b versus IVM1c), ECOG Performance status (0 versus 1) and prior treatment with any number of lines of immunotherapy for unresectable or metastatic disease (yes versus no).

Pre-assignment

Screening details:

Patients signed a specific informed consent for NRAS mutation analysis at a central laboratory. Patients with documented NRAS Q61 mutation result were eligible for screening.

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study was open label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Binimetinib

Arm description:

Patients were assigned to one of the following 2 treatment arms in a ratio of 2:1 in favor of the investigational treatment:

- Binimetinib (MEK162) 45 mg orally bid (twice a day)

- Dacarbazine 1000 mg/m2 IV once q3w (every 3 weeks)

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The investigational treatment was binimetinib (MEK162) 45 mg orally bid (twice a day) and the control treatment was dacarbazine 1000 mg/m2 IV once q3w (every 3 weeks). Binimetinib 15-mg film-coated tablets were supplied to the Investigators by the Sponsor.
MEK162 was administered as a fixed dose of 45 mg (3 x 15 mg tablets) BID, with a glass of water. Patients were fasted 1 hour before and after the dose. Patients were supplied with a sufficient number of tablets for the number of doses to be taken prior to the next scheduled visit. Prescribed doses were taken twice daily, approximately 12 ± 2 hrs apart.
It was recommended to document whether each prescribed dose was taken or not in the MEK162 patient dosing diary.
If a patient vomited at any time after dosing, the dose of study drug had not been re-administered. Doses of study drug omitted for AEs or any other reason had not made up later in the day, or at the end of the dosing period.

Arm title	Dacarbazine

Arm description:

Patients were assigned to one of the following 2 treatment arms in a ratio of 2:1 in favor of the investigational treatment:

- Binimetinib (MEK162) 45 mg orally bid (twice a day)

- Dacarbazine 1000 mg/m2 IV once q3w (every 3 weeks)

Arm type	Active comparator
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients randomized to dacarbazine (or locally approved generics) will receive an IV infusion of dacarbazine 1000 mg/m2 over the course of 1 hour on day 1 and then every three weeks.
Body surface area (BSA), in m2, was calculated using the following formula, where weight (W) is in kilograms and height (H) is in centimeters (Dubois and Dubois 1916):
BSA= (W0.425x H0.725) x 0.007184

Globally, dacarbazine was available in vials containing 100 mg, 200 mg, 500 mg and 1000 mg. Dacarbazine (vials of 100mg/200mg/500mg/ 1000mg) was reconstituted according to local practice and following the guidelines in the local labels.

Dacarbazine should be reconstituted according to local practice and following the guidelines in the local labels.

Number of subjects in period 1	Binimetinib	Dacarbazine
Started	269	133
Completed	0	0
Not completed	269	133
Physician decision	24	13
Patient decision	-	19
Death	10	1
Other	-	1
Adverse event	66	8
Progressive disease	142	76
Subject/guardian decision	26	14
Protocol deviation	1	1

Baseline characteristics

Reporting groups

Reporting group title	Binimetinib

Reporting group description:

Patients were assigned to one of the following 2 treatment arms in a ratio of 2:1 in favor of the investigational treatment:

- Binimetinib (MEK162) 45 mg orally bid (twice a day)

- Dacarbazine 1000 mg/m2 IV once q3w (every 3 weeks)

Reporting group title	Dacarbazine

Reporting group description:

Patients were assigned to one of the following 2 treatment arms in a ratio of 2:1 in favor of the investigational treatment:

- Binimetinib (MEK162) 45 mg orally bid (twice a day)

- Dacarbazine 1000 mg/m2 IV once q3w (every 3 weeks)

Reporting group values	Binimetinib	Dacarbazine	Total
Number of subjects	269	133	402
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	130	80	210
From 65-84 years	139	53	192
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	103	48	151
Male	166	85	251

End points

End points reporting groups

Reporting group title	Binimetinib

Reporting group description:

Patients were assigned to one of the following 2 treatment arms in a ratio of 2:1 in favor of the investigational treatment:

- Binimetinib (MEK162) 45 mg orally bid (twice a day)

- Dacarbazine 1000 mg/m2 IV once q3w (every 3 weeks)

Reporting group title	Dacarbazine

Reporting group description:

Patients were assigned to one of the following 2 treatment arms in a ratio of 2:1 in favor of the investigational treatment:

- Binimetinib (MEK162) 45 mg orally bid (twice a day)

- Dacarbazine 1000 mg/m2 IV once q3w (every 3 weeks)

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Full analysis set included all patients randomized

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival (PFS), defined as the time from the date of randomization to the date of the first documented disease progression or death due
to any cause, whichever occurs first. PFS was determined based on tumor assessment (RECIST V1.1 criteria) as per BIRC and survival information.
Disease progression was determined based on tumor assessment according to RECIST v1.1.
The local Investigator's assessments was used as supportive analyses.

The median follow-up time for PFS per central review was 2.69 months for the binimetinib arm and 1.45 months for the dacarbazine arm. 38% risk reduction in disease progression or death (PFS) was observed for patients treated with binimetinib compared to those treated with dacarbazine.

End point type	Primary

End point timeframe:

The time from the date of randomization to the date of the first documented disease progression or death due to any cause, whichever occurs first.

End point values	Binimetinib	Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	133		
Units: months				
median (confidence interval 95%)	2.83 (2.76 to 3.55)	1.51 (1.48 to 1.71)		

Statistical analyses

Statistical analysis title	Comparison of the distribution of PFS

Statistical analysis description:

The primary efficacy analysis was the comparison of the distribution of PFS between the 2 treatment arms using a stratified log-rank test at one-sided 2.5% cumulative level of significance. The null and the alternative hypothesis were defined as follows:
H01: $S1T(t) \leq S1C(t)$ vs. HA1: $S1T(t) > S1C(t)$, $t \geq 0$

where S1C(t) was the survival distribution function of PFS in the control arm (dacarbazine) and S1T(t) was the survival distribution function of PFS in the experimental arm (binimetinib).

Comparison groups	Binimetinib v Dacarbazine
Number of subjects included in analysis	402
Analysis specification	Post-hoc
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.8
Variability estimate	Standard deviation

Notes:

[1] - The primary efficacy endpoint, PFS as per BIRC, was analyzed based on the data from the FAS (full analysis set) according to the treatment arm and the stratification factors patients were randomized to.
[2] - P-value was obtained from the one-sided stratified log-rank test except in the comparison labeled "unstratified tests".

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of the treatment period until 30 days of the last study medication dose.

An overview of AEs , which included Adverse events of special interest (AESIs) was summarized by SOC and PT.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Binimetinib
Reporting group description: -	
Reporting group title	Dacarbazine
Reporting group description: -	

Serious adverse events	Binimetinib	Dacarbazine	
Total subjects affected by serious adverse events			
subjects affected / exposed	95 / 269 (35.32%)	26 / 114 (22.81%)	
number of deaths (all causes)	24	3	
number of deaths resulting from adverse events	4	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haemorrhage			

subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dilatation			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	10 / 269 (3.72%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary pain			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			

subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 269 (0.37%)	3 / 114 (2.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 269 (0.37%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 269 (1.49%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 269 (1.12%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			

subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal behaviour			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 269 (1.12%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemoglobin decreased			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraocular pressure increased			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle injury			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial flutter			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve disease			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	1 / 269 (0.37%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dropped head syndrome			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor dysfunction			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenic syndrome			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 269 (0.37%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive supranuclear palsy			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			

subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 269 (0.00%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	4 / 269 (1.49%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein thrombosis			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 269 (1.12%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 269 (0.37%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune pancreatitis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			

subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperhidrosis			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 269 (0.00%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			

subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Skin infection			
subjects affected / exposed	3 / 269 (1.12%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 269 (0.74%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Soft tissue infection			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermo-hypodermitis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	0 / 269 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 269 (0.74%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 269 (0.37%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Binimetinib	Dacarbazine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	269 / 269 (100.00%)	104 / 114 (91.23%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	36 / 269 (13.38%)	4 / 114 (3.51%)	
occurrences (all)	36	4	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	97 / 269 (36.06%)	5 / 114 (4.39%)	
occurrences (all)	97	5	

Fatigue			
subjects affected / exposed	68 / 269 (25.28%)	38 / 114 (33.33%)	
occurrences (all)	68	38	
Asthenia			
subjects affected / exposed	44 / 269 (16.36%)	19 / 114 (16.67%)	
occurrences (all)	44	19	
Pyrexia			
subjects affected / exposed	34 / 269 (12.64%)	16 / 114 (14.04%)	
occurrences (all)	34	16	
Peripheral swelling			
subjects affected / exposed	15 / 269 (5.58%)	2 / 114 (1.75%)	
occurrences (all)	15	2	
Face oedema			
subjects affected / exposed	14 / 269 (5.20%)	0 / 114 (0.00%)	
occurrences (all)	14	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	27 / 269 (10.04%)	5 / 114 (4.39%)	
occurrences (all)	27	5	
Cough			
subjects affected / exposed	20 / 269 (7.43%)	10 / 114 (8.77%)	
occurrences (all)	20	10	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 269 (6.32%)	8 / 114 (7.02%)	
occurrences (all)	17	8	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	119 / 269 (44.24%)	3 / 114 (2.63%)	
occurrences (all)	119	3	
Aspartate aminotransferase increased			
subjects affected / exposed	39 / 269 (14.50%)	5 / 114 (4.39%)	
occurrences (all)	39	5	
Ejection fraction decreased			

subjects affected / exposed	39 / 269 (14.50%)	2 / 114 (1.75%)	
occurrences (all)	39	2	
Alanine aminotransferase increased			
subjects affected / exposed	23 / 269 (8.55%)	8 / 114 (7.02%)	
occurrences (all)	23	8	
Intraocular pressure increased			
subjects affected / exposed	19 / 269 (7.06%)	0 / 114 (0.00%)	
occurrences (all)	19	0	
Weight decreased			
subjects affected / exposed	13 / 269 (4.83%)	6 / 114 (5.26%)	
occurrences (all)	13	6	
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 269 (2.97%)	7 / 114 (6.14%)	
occurrences (all)	8	7	
Platelet count decreased			
subjects affected / exposed	2 / 269 (0.74%)	11 / 114 (9.65%)	
occurrences (all)	2	11	
Neutrophil count decreased			
subjects affected / exposed	1 / 269 (0.37%)	8 / 114 (7.02%)	
occurrences (all)	1	8	
Nervous system disorders			
Neck pain			
subjects affected / exposed	17 / 269 (6.32%)	2 / 114 (1.75%)	
occurrences (all)	17	2	
Dysgeusia			
subjects affected / exposed	21 / 269 (7.81%)	2 / 114 (1.75%)	
occurrences (all)	21	2	
Headache			
subjects affected / exposed	18 / 269 (6.69%)	9 / 114 (7.89%)	
occurrences (all)	18	9	
Dizziness			
subjects affected / exposed	17 / 269 (6.32%)	3 / 114 (2.63%)	
occurrences (all)	17	3	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	19 / 269 (7.06%)	11 / 114 (9.65%)	
occurrences (all)	19	11	
Lymphopenia			
subjects affected / exposed	7 / 269 (2.60%)	7 / 114 (6.14%)	
occurrences (all)	7	7	
Neutropenia			
subjects affected / exposed	4 / 269 (1.49%)	21 / 114 (18.42%)	
occurrences (all)	4	21	
Thrombocytopenia			
subjects affected / exposed	2 / 269 (0.74%)	17 / 114 (14.91%)	
occurrences (all)	2	17	
Leukopenia			
subjects affected / exposed	0 / 269 (0.00%)	8 / 114 (7.02%)	
occurrences (all)	0	8	
Eye disorders			
Retinal detachment			
subjects affected / exposed	35 / 269 (13.01%)	0 / 114 (0.00%)	
occurrences (all)	35	0	
Eyelid oedema			
subjects affected / exposed	28 / 269 (10.41%)	0 / 114 (0.00%)	
occurrences (all)	28	0	
Vision blurred			
subjects affected / exposed	20 / 269 (7.43%)	1 / 114 (0.88%)	
occurrences (all)	20	1	
Subretinal fluid			
subjects affected / exposed	19 / 269 (7.06%)	0 / 114 (0.00%)	
occurrences (all)	19	0	
Macular oedema			
subjects affected / exposed	17 / 269 (6.32%)	0 / 114 (0.00%)	
occurrences (all)	17	0	
Periorbital oedema			
subjects affected / exposed	14 / 269 (5.20%)	0 / 114 (0.00%)	
occurrences (all)	14	0	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	109 / 269 (40.52%)	15 / 114 (13.16%)	
occurrences (all)	109	15	
Nausea			
subjects affected / exposed	85 / 269 (31.60%)	35 / 114 (30.70%)	
occurrences (all)	85	35	
Vomiting			
subjects affected / exposed	58 / 269 (21.56%)	15 / 114 (13.16%)	
occurrences (all)	58	15	
Constipation			
subjects affected / exposed	39 / 269 (14.50%)	22 / 114 (19.30%)	
occurrences (all)	39	22	
Dry mouth			
subjects affected / exposed	22 / 269 (8.18%)	1 / 114 (0.88%)	
occurrences (all)	22	1	
Abdominal pain			
subjects affected / exposed	24 / 269 (8.92%)	8 / 114 (7.02%)	
occurrences (all)	24	8	
Abdominal pain upper			
subjects affected / exposed	16 / 269 (5.95%)	3 / 114 (2.63%)	
occurrences (all)	16	3	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	96 / 269 (35.69%)	2 / 114 (1.75%)	
occurrences (all)	96	2	
Dry skin			
subjects affected / exposed	37 / 269 (13.75%)	2 / 114 (1.75%)	
occurrences (all)	37	2	
Pruritus			
subjects affected / exposed	27 / 269 (10.04%)	2 / 114 (1.75%)	
occurrences (all)	27	2	
Skin fissures			
subjects affected / exposed	26 / 269 (9.67%)	0 / 114 (0.00%)	
occurrences (all)	26	0	
Alopecia			

subjects affected / exposed	24 / 269 (8.92%)	3 / 114 (2.63%)	
occurrences (all)	24	3	
Rash maculo-papular			
subjects affected / exposed	23 / 269 (8.55%)	0 / 114 (0.00%)	
occurrences (all)	23	0	
Erythema			
subjects affected / exposed	17 / 269 (6.32%)	2 / 114 (1.75%)	
occurrences (all)	17	2	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	28 / 269 (10.41%)	3 / 114 (2.63%)	
occurrences (all)	28	3	
Back pain			
subjects affected / exposed	19 / 269 (7.06%)	6 / 114 (5.26%)	
occurrences (all)	19	6	
Arthralgia			
subjects affected / exposed	18 / 269 (6.69%)	3 / 114 (2.63%)	
occurrences (all)	18	3	
Muscular weakness			
subjects affected / exposed	16 / 269 (5.95%)	0 / 114 (0.00%)	
occurrences (all)	16	0	
Pain in extremity			
subjects affected / exposed	11 / 269 (4.09%)	6 / 114 (5.26%)	
occurrences (all)	11	6	
Infections and infestations			
Rash pustular			
subjects affected / exposed	18 / 269 (6.69%)	0 / 114 (0.00%)	
occurrences (all)	18	0	
Nasopharyngitis			
subjects affected / exposed	17 / 269 (6.32%)	5 / 114 (4.39%)	
occurrences (all)	17	5	
Erysipelas			
subjects affected / exposed	15 / 269 (5.58%)	0 / 114 (0.00%)	
occurrences (all)	15	0	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	34 / 269 (12.64%)	19 / 114 (16.67%)	
occurrences (all)	34	19	
Hypokalaemia			
subjects affected / exposed	12 / 269 (4.46%)	0 / 114 (0.00%)	
occurrences (all)	12	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2013	Protocol amendment V 01 All sections of the protocol including the protocol title that describe the patient population: • Changed the patient population to reflect the inclusion of patients who had progressed on or after prior first-line immunotherapy for metastatic disease. • All section of the protocol were updated with the appropriate visit window exception for the visit occurring 6 weeks after randomization (Study Day 43). The appropriate window is now +3 days • Table 6-6 MEK162-Recommended dose modifications associated with treatment related adverse events •Synopsis, Sections 2.2, 4.1 and 6.6.2 added a stratification factor to stratify patients by first-line immunotherapy (yes versus no) • Synopsis and Section 5.2 added patients who had progressed on or after prior first-line immunotherapy for metastatic disease to inclusion #5 Synopsis and Section 5.3: • Added history of retinal degenerative disease as exclusion #5 • Added patients who have received more than one line of immunotherapy for metastatic melanoma as exclusion #10 • Added patients who have not met the minimal washout requirements for prior metastatic therapy as exclusion #11 • Revised exclusion criterion #12 to exclude prior chemotherapy treatment • Clarified exclusion criterion #13 to not include atrial fibrillation and paroxysmal supraventricular hypertension as exclusionary as significant cardiac arrhythmias • Updated the uncontrolled arterial hypertension exclusion criteria to make it less specific (criterion #14)
03 September 2013	Protocol amendment V 02 included: • Update the inclusion and exclusion criteria • New and modify existing safety monitoring • Improvement some operational aspects • Other (clarifications, administrative changes and corrections)

07 April 2014	Protocol amendment V 03 included the following updates: • Clarifications of the eligibility criteria • Improvement operational aspects of the trial • Other (clarifications and corrections) Section 1.2.1.2 • Added "For updated clinical safety and efficacy data please refer to the most recent version of the Investigator's Brochure." To clinical experience Section 1.2.1.3 • Added results from the food effect study CMEK162A2103 Section 4.1 • Added "using the same IDE test for prescreening that is used in this protocol, and who have consented to utilizing those results for this study" • Added "Regardless of whether additional tumor is needed for the required study analyses, all patients intending to participate in the CMEK162A2301 study must sign both the prescreening and main consents" Section 5.2: • Added "or unknown primary" and "(Uveal and mucosa melanoma are excluded)" to inclusion criterion # 3 • Remove the word "first-line" from inclusion criterion #5 • Reduced the hemoglobin value from 10g/dL to 9g/dL in inclusion criterion # 8 • Added a "triplicate average baseline" to QTcF reading at baseline to the inclusion criterion # 9 Section 5.3: • Removed the word "active" and "(i.e. those with radiographically unresectable, symptomatic lesions)", "and", "are eligible if the" from exclusion criterion # 1 • Added the words "untreated" "are eligible if a)" ,"all known CNS lesions have been", "and b) after treatment" to exclusion criterion # 1 • Removed "non-cutaneous" and Added "Uveal or mucosal " melanoma to exclusion criterion # 2 • Removed exclusion criterion # 10
09 October 2014	Protocol amendment V 04 - The main objectives of this amendment were: • To make mandatory ocular coherence tomography (OCT) assessments at each visit to better characterize retinal events Safety: • To modify the grading criteria and dose modification for retinal events • To clarify the dose modification table for left ventricular systolic dysfunction • To clarify the guidance for monitoring and dose modification for CK elevation • To update and clarify eligibility criteria • To improve operational aspects of the trial • Other (clarifications and corrections)
26 October 2015	Protocol amendment V 05 - the purpose of this amendment is to document a change in study sponsorship from Novartis to Array BioPharma. Study design and procedures are not affected.

05 December 2018	Protocol amendment V 06 - this protocol amendment decreases the frequency of assessments for those patients continuing to receive binimetinib. In addition, as no further analyses of progression-free survival (PFS) and overall survival (OS) were planned, post-treatment disease follow-up and survival follow-up assessments would not be performed and central review of tumor assessments would be discontinued. Section 4.1 • Efficacy assessments will be performed locally, per standard of care for patients with advanced/metastatic melanoma, and tumor imaging will no longer be sent to the blinded independent review committee (BIRC) • Treatment discontinuation due to disease progression will now be based on Investigator assessment rather than BIRC determination • At the safety follow-up visit, patients will only complete assessment for adverse events (AEs) and serious adverse events (SAEs) and no other follow-up assessments outlined in prior amendments will be completed (i.e. health-related quality of life,survival follow-up) • Definition of study completion was updated Section 4.3 • The definition for the end of study was updated Section 6.2 • The assessment of progressive disease (PD) and discontinuation of study treatment would be based on Investigator assessment Section 6.7.2 • Study drug would no longer be dispensed by Interactive Response Technology (IRT), but would be provided by Fisher and manually assigned to the patients by site personnel.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported