Clinical trial results:
An Open-label Phase 1b/2 Study of Binimetinib Administered in Combination with Nivolumab or Nivolumab Plus Ipilimumab in Patients with Previously Treated Microsatellite-stable (MSS) Metastatic Colorectal Cancer with RAS Mutation

Summary

EudraCT number	2017-003464-12
Trial protocol	GB ES NL BE
Global end of trial date	25 February 2021

Results information

Result version number	v1 (current)
This version publication date	12 February 2022
First version publication date	12 February 2022

Trial information

Trial identification

Sponsor protocol code	ARRAY-162-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03271047
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, United States
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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	28 July 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1b:
1. Determine the MTD and RP2D of binimetinib administered in combination with nivolumab
2. Determine the MTD and RP2D of binimetinib administered in combination with nivolumab plus ipilimumab

Phase 2:
Assess the preliminary antitumor activity of the treatment combinations based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 October 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	75
EEA total number of subjects	47

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)	53
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included 2 phases: Phase 1b and Phase 2. The recommended dose for Phase 2 (RP2D) of binimetinib was determined in Phase 1b (dose finding phase). Total 75 subjects were enrolled in 22 sites in 5 countries. Study started from 18 October 2017 and completed on 25 February 2021.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b: Nivolumab+Binimetinib

Arm description:

Subjects with previously treated microsatellite-stable (MSS) metastatic colorectal cancer with rat sarcoma virus (RAS) mutation received binimetinib at a starting dose of 45 milligrams (mg) tablet orally twice daily (BID) along with 480 mg intravenous (IV) dose of nivolumab every 4 weeks in each 28 day treatment cycle. Binimetinib dose modification to intermitted dosing (3 weeks on treatment and 1 week off treatment) with 45 mg dose or dose reduction to 30 mg BID or 30 mg intermittent dosing based on investigator’s decision as per its tolerability among subjects. Subjects then followed up for safety for around 150 days.

Arm type	Experimental
Investigational medicinal product name	Binimetinib and Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Injection
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Subjects received binimetinib at a starting dose of 45 mg tablet orally BID along with nivolumab 480 mg IV every 4 weeks in each 28 day treatment cycle.

Arm title	Phase 1b: Nivolumab+Ipilimumab+Binimetinib

Arm description:

Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received binimetinib at a starting dose of 45 mg tablet BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle. Ipilimumab was administered at the dose of 1 milligram per kilogram (mg/kg) IV every 8 weeks after completion of nivolumab infusion. Binimetinib dose modification to intermitted dosing (3 weeks on treatment and 1 week off treatment) with 45 mg dose or dose reduction to 30 mg BID or 30 mg intermittent dosing based on investigator’s decision as per its tolerability among subjects. Subjects then followed up for safety for around 150 days.

Arm type	Experimental
Investigational medicinal product name	Binimetinib, Nivolumab and Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Injection
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Subjects received binimetinib at a starting dose of 45 mg tablet BID along with nivolumab 480 mg IV dose every 4 weeks in each 28 day treatment cycle. Ipilimumab was administered at the dose of 1 mg/kg IV every 8 weeks after completion of nivolumab infusion.

Arm title	Phase 2: Nivolumab+Binimetinib

Arm description:

Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received 45 mg binimetinib tablet orally BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle, until disease progression, unacceptable toxicity, withdrawal of informed consent, initiation of subsequent anticancer therapy, lost to follow-up or death. Subjects then followed up for safety for around 150 days.

Arm type	Experimental
Investigational medicinal product name	Binimetinib and Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Injection
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Subjects received 45 mg binimetinib tablet orally BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle.

Arm title	Phase 2: Nivolumab+Ipilimumab+Binimetinib

Arm description:

Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received 45 mg binimetinib tablet orally BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle. Ipilimumab was administered at the dose of 1 mg/kg IV every 8 weeks after completion of nivolumab infusion until disease progression, unacceptable toxicity, withdrawal of informed consent, initiation of subsequent anticancer therapy, lost to follow-up or death. Subjects then followed up for safety for around 150 days.

Arm type	Experimental
Investigational medicinal product name	Binimetinib, Nivolumab and Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Injection
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Subjects received binimetinib 45 mg tablet orally BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle. Ipilimumab was administered at the dose of 1 mg/kg IV every 8 weeks after completion of nivolumab infusion.

Number of subjects in period 1	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Binimetinib
Started	10	11	27
Completed	0	0	0
Not completed	10	11	27
Death	8	8	20
Completed follow-up per protocol	1	1	-
Unspecified	-	-	-
Consent withdrawn by subject	-	2	5
Lost to follow-up	1	-	2

Number of subjects in period 1	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Started	27

Completed	0
Not completed	27
Death	21
Completed follow-up per protocol	4
Unspecified	1
Consent withdrawn by subject	-
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1b: Nivolumab+Binimetinib
Reporting group description:	
Subjects with previously treated microsatellite-stable (MSS) metastatic colorectal cancer with rat sarcoma virus (RAS) mutation received binimetinib at a starting dose of 45 milligrams (mg) tablet orally twice daily (BID) along with 480 mg intravenous (IV) dose of nivolumab every 4 weeks in each 28 day treatment cycle. Binimetinib dose modification to intermitted dosing (3 weeks on treatment and 1 week off treatment) with 45 mg dose or dose reduction to 30 mg BID or 30 mg intermittent dosing based on investigator's decision as per its tolerability among subjects. Subjects then followed up for safety for around 150 days.	
Reporting group title	Phase 1b: Nivolumab+Ipilimumab+Binimetinib
Reporting group description:	
Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received binimetinib at a starting dose of 45 mg tablet BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle. Ipilimumab was administered at the dose of 1 milligram per kilogram (mg/kg) IV every 8 weeks after completion of nivolumab infusion. Binimetinib dose modification to intermitted dosing (3 weeks on treatment and 1 week off treatment) with 45 mg dose or dose reduction to 30 mg BID or 30 mg intermittent dosing based on investigator's decision as per its tolerability among subjects. Subjects then followed up for safety for around 150 days.	
Reporting group title	Phase 2: Nivolumab+Binimetinib
Reporting group description:	
Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received 45 mg binimetinib tablet orally BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle, until disease progression, unacceptable toxicity, withdrawal of informed consent, initiation of subsequent anticancer therapy, lost to follow-up or death. Subjects then followed up for safety for around 150 days.	
Reporting group title	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Reporting group description:	
Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received 45 mg binimetinib tablet orally BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle. Ipilimumab was administered at the dose of 1 mg/kg IV every 8 weeks after completion of nivolumab infusion until disease progression, unacceptable toxicity, withdrawal of informed consent, initiation of subsequent anticancer therapy, lost to follow-up or death. Subjects then followed up for safety for around 150 days.	

Reporting group values	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Binimetinib
Number of subjects	10	11	27
Age Categorical Units: Subjects			
18-64 years	5	9	19
65-84 years	5	2	8
Sex: Female, Male Units: Subjects			
Female	2	4	11
Male	8	7	16
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1

White	9	11	21
Unknown or Not Reported	0	0	0
Others	0	0	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	1
Not Hispanic or Latino	10	11	21
Unknown	0	0	1
Not Reported	0	0	4

Reporting group values	Phase 2: Nivolumab+Ipilimumab+Binimetinib	Total	
Number of subjects	27	75	
Age Categorical Units: Subjects			
18-64 years	20	53	
65-84 years	7	22	
Sex: Female, Male Units: Subjects			
Female	10	27	
Male	17	48	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	3	
White	23	64	
Unknown or Not Reported	0	0	
Others	3	7	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	
Not Hispanic or Latino	23	65	
Unknown	0	1	
Not Reported	4	8	

End points

End points reporting groups

Reporting group title	Phase 1b: Nivolumab+Binimetinib

Reporting group description:

Subjects with previously treated microsatellite-stable (MSS) metastatic colorectal cancer with rat sarcoma virus (RAS) mutation received binimetinib at a starting dose of 45 milligrams (mg) tablet orally twice daily (BID) along with 480 mg intravenous (IV) dose of nivolumab every 4 weeks in each 28 day treatment cycle. Binimetinib dose modification to intermitted dosing (3 weeks on treatment and 1 week off treatment) with 45 mg dose or dose reduction to 30 mg BID or 30 mg intermittent dosing based on investigator's decision as per its tolerability among subjects. Subjects then followed up for safety for around 150 days.

Reporting group title	Phase 1b: Nivolumab+Ipilimumab+Binimetinib

Reporting group description:

Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received binimetinib at a starting dose of 45 mg tablet BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle. Ipilimumab was administered at the dose of 1 milligram per kilogram (mg/kg) IV every 8 weeks after completion of nivolumab infusion. Binimetinib dose modification to intermitted dosing (3 weeks on treatment and 1 week off treatment) with 45 mg dose or dose reduction to 30 mg BID or 30 mg intermittent dosing based on investigator's decision as per its tolerability among subjects. Subjects then followed up for safety for around 150 days.

Reporting group title	Phase 2: Nivolumab+Binimetinib

Reporting group description:

Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received 45 mg binimetinib tablet orally BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle, until disease progression, unacceptable toxicity, withdrawal of informed consent, initiation of subsequent anticancer therapy, lost to follow-up or death. Subjects then followed up for safety for around 150 days.

Reporting group title	Phase 2: Nivolumab+Ipilimumab+Binimetinib

Reporting group description:

Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received 45 mg binimetinib tablet orally BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle. Ipilimumab was administered at the dose of 1 mg/kg IV every 8 weeks after completion of nivolumab infusion until disease progression, unacceptable toxicity, withdrawal of informed consent, initiation of subsequent anticancer therapy, lost to follow-up or death. Subjects then followed up for safety for around 150 days.

Primary: Phase 2: Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1

End point title	Phase 2: Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1[1][2]

End point description:

ORR:percentage of subjects who achieved best overall response(BOR) of complete response(CR)/partial response(PR) determined by investigator per RECISTv1.1.CR:disappearance of target and non-target lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures less than (<)10 millimeter(mm). PR: >=30%decrease in sum of measures(longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference baseline sum of diameters. Non-target lesions must be non-progressive disease(PD).PD: >=20%increase in sum of diameters of target lesions, taking as reference smallest sum on study. In addition to relative increase of 20%, sum must demonstrate absolute increase of >=5mm. Appearance of one/more new lesions considered progression. All subjects randomized to study treatment in Phase 2. -99999, 99999=Lower, upper limit of 95%confidence interval(CI) not estimable,as there were no subjects with event in this reporting group.

End point type	Primary

End point timeframe:

From start of the treatment until disease progression, death or initiation of new anticancer therapy, whichever occurred first (Phase 2: maximum up to 26 months approximately)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was summarized for Phase 2: Nivolumab+Binimetinib and Phase 2: Nivolumab+Ipilimumab+Binimetinib reporting arms only.

End point values	Phase 2: Nivolumab+Binimetinib	Phase 2: Nivolumab+Ipilimumab+Binimetinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: Percentage of subjects				
number (confidence interval 95%)	0.0 (-99999 to 99999)	7.4 (0.9 to 24.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Number of Subjects With Dose-Limiting Toxicities (DLT)

End point title	Phase 1b: Number of Subjects With Dose-Limiting Toxicities (DLT)[3][4]

End point description:

DLT:AE/abnormal laboratory assessed unrelated-disease,disease progression,intercurrent illness/concomitant medication/therapies resulting inability tolerate 75%dose intensity in Cycle(C)1.Total bilirubin(TBL)grade(G)>=3(>3.0*upper limit of normal[ULN)]);AST/ALT>5-8*ULN>5days(D),>8*ULN,>3*ULN concurrent TBL>2*ULN;G>=3 serum creatinine,CK elevation,ECG QTcF prolonged,G3 troponin,electrolyte>72hours(hrs),G3/4 amylase/lipase.G4ANC,platelet count(PC)>7D;G3/4PC,other AE except lymphopenia.G>=3retinopathy,other disorder>21D;G2uveitis/eye pain/blurred vision/decreased visual acuity;G4 other disorder.Decrease LVEF>10% G>=3cardiac disorders.G3/4hypertension.G3fatigue>=7D,hypersensitivity,infusion reaction,fever>=72hrs/haemodynamic compromise,endocrinopathy.G>=2interstitial lung disease/pneumonitis;G3bronchospasm.G3/4rash,hand foot skin reaction,photosensitivity.G3colitis;G3/4diarrhea,nausea/vomiting.NeurologicG3.Other

End point type	Primary

End point timeframe:

Cycle 1: Day 1 up to Day 28

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was summarized for Phase 1b: Nivolumab+Binimetinib and Phase 1b: Nivolumab+Ipilimumab+Binimetinib reporting arms only.

End point values	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	11		
Units: Subjects	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Objective Response Rate (ORR) per RECIST v1.1

End point title	Phase 1b: Objective Response Rate (ORR) per RECIST v1.1[5]

End point description:

ORR: percentage of subjects who achieved a BOR of CR or PR as determined by investigator per RECIST v1.1. As per RECIST v1.1, CR: disappearance of target and non-target lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures <10 mm. PR: >=30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD. PD: >=20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. All subjects who received at least 1 dose of any study treatment in Phase 1b. -99999 and 99999=Lower and upper limit of 95%CI not estimable, as there were no subjects who had event in this reporting group.

End point type	Secondary

End point timeframe:

From start of the treatment until disease progression, death or initiation of new anticancer therapy, whichever occurred first (Phase 1b: maximum up to 9 months approximately)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was summarized for Phase 1b: Nivolumab+Binimetinib and Phase 1b: Nivolumab+Ipilimumab+Binimetinib reporting arms only.

End point values	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: Percentage of subjects				
number (confidence interval 95%)	0.0 (-99999 to 99999)	0.0 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as per RECIST v1.1

End point title	Duration of Response (DOR) as per RECIST v1.1

End point description:

DOR:time between date of first documented confirmed response(PR/CR)and date of first documented progression/death due to any cause. CR:disappearance of target and non-target lesions and normalization of tumour markers. Pathological lymph nodes short axis measures <10mm. PR:>=30% decrease in sum of measures(tumour lesions-longest diameter and nodes-short axis)of target lesions, taking as reference baseline sum of diameters. PD: >=20% increase in sum of diameters of measured lesions taking as references smallest sum of diameters recorded on study(including baseline),absolute increase of >=5mm/appearance of at least 1new lesion. Unequivocal progression of existing non-target lesions. FAS:all subjects who received at least 1dose of any study drug in Phase1b and all subjects randomized to study treatment in Phase2.'Number of subjects analysed':signifies number of subjects who achieved an objective response.No subjects had event in Phase1b and Nivolumab and Binimetinib group of Phase2.

End point type	Secondary

End point timeframe:

From date of first documented CR/PR to date of first documented PD, death or initiation of new anticancer therapy, whichever occurred first (Phase 1b: maximum up to 9 months approximately, Phase 2: maximum up to 26 months approximately)

End point values	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Binimetinib	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[6]	0[7]	0[8]	2
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	11.4 (7.5 to 15.2)

Notes:

[6] - No subjects had event in Phase 1b: Nivolumab+ Binimetinib.

[7] - No subjects had event in Phase 1b: Nivolumab+Ipilimumab+Binimetinib.

[8] - No subjects had event in Phase 2: Nivolumab+Binimetinib.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Complete Response as per RECIST v1.1

End point title	Percentage of Subjects With Complete Response as per RECIST v1.1

End point description:

Complete response as per RECIST v1.1 was defined as disappearance of target and non-target lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures <10 mm. Full analysis set (FAS) included all subjects who received at least 1 dose of any study drug in Phase 1b and all subjects randomized to study treatment in Phase 2.

End point type	Secondary

End point timeframe:

From start of the treatment until disease progression, death or initiation of new anticancer therapy, whichever occurred first (Phase 1b: maximum up to 9 months approximately and Phase 2: maximum up to 26 months approximately)

End point values	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Binimetinib	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	27	27
Units: Percentage of subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAE) Based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAE) Based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03

End point description:

AE:any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE:AE resulting in any of following outcomes/deemed significant for any other reason: death; initial /prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. TEAEs:events between first dose of study drug and up to 30days after last dose or before start of new anticancer therapy minus 1day, whichever occurred first. TEAE graded by CTCAE grade 4.03: G3:severe/medically significant but not immediately life-threatening/hospitalization/prolongation of existing hospitalization indicated/disabling/limiting self-care activities of daily living(ADL); G4:life-threatening consequence/urgent intervention indicated. In this endpoint, number of subjects with 'all grades' and 'G3/4' were reported. Safety set: all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From start of the treatment up to 30 days after last dose or start of new anticancer therapy minus 1 day, whichever occurred first (Phase 1b: maximum up to 9 months approximately and Phase 2: maximum up to 26 months approximately)

End point values	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Binimetinib	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	27	27
Units: Subjects				
Treatment emergent AEs- All grades	10	11	27	27
Treatment emergent SAEs- All grades	5	6	12	11
Treatment emergent AEs- Grade 3/4	6	8	19	21
Treatment emergent SAEs- Grade 3/4	5	6	11	10

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift From Baseline in Laboratory Parameter Values Based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03: Haematology and Coagulation

End point title	Number of Subjects With Shift From Baseline in Laboratory Parameter Values Based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03: Haematology and Coagulation

End point description:

Haematology parameters: Haemoglobin (Hb) graded high, Hb graded low, platelets count graded low, white blood cell (WBC) graded high, WBC graded low, neutrophils graded low, lymphocytes graded high, lymphocytes graded low. Coagulation parameters: International normalized ratio (INR) graded high, activated partial thromboplastin time (aPTT) graded high. Test abnormalities were graded by CTCAE v4.03 as Grade 1=mild; Grade 2=moderate; Grade 3/Grade 4=severe/life-threatening. A grade 0 was assigned for all non-missing values not graded as 1 or higher. If value was graded >=1 but falls within the normal range, the grade was reset to 0. Categories with at least 1 non-zero data values are reported. Safety set included of all subjects who received at least 1 dose of study drug. Here "n": subjects evaluable for this endpoint for specified rows. Baseline=BL, Postbaseline=PBL, Missing=M. '99999' signifies data not available as none of the subjects were evaluable for specified categories.

End point type	Secondary

End point timeframe:

Phase 1b: Baseline up to 30 days after last dose (maximum up to 9 months approximately), Phase 2: Baseline up to 30 days after last dose (maximum up to 26 months approximately)

End point values	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Binimetinib	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	27	27
Units: Subjects				
Haemoglobin-Low G:G0(BL) to G0(PBL) n=7,6,13,16	3	3	4	5
Haemoglobin-Low G:G0(BL) to G1(PBL) n=7,6,13,16	2	2	6	10
Haemoglobin-Low G:G0(BL) to G2(PBL) n=7,6,13,16	2	1	2	1
Haemoglobin-Low G:G0(BL) to G3(PBL) n=7,6,13,16	0	0	1	0
Haemoglobin-Low G:G1(BL) to G0(PBL) n=3,5,10,6	0	0	1	0
Haemoglobin-Low G:G1(BL) to G1(PBL) n=3,5,10,6	1	4	4	4
Haemoglobin-Low G:G1(BL) to G2(PBL) n=3,5,10,6	2	0	3	1
Haemoglobin-Low G:G1(BL) to G3(PBL) n=3,5,10,6	0	1	1	1
Haemoglobin-Low G:G1(BL) to M(PBL) n=3,5,10,6	0	0	1	0
Haemoglobin-Low G:G2(BL) to G2(PBL) n=0,0,4,5	99999	99999	3	5
Haemoglobin-Low G:G2(BL) to G3(PBL) n=0,0,4,5	99999	99999	1	0
Haemoglobin-High G:G0(BL) to G0(BL) n=10,11,27,27	10	11	26	26
Haemoglobin-High G:G0(BL) to G1(PBL) n=10,11,27,27	0	0	0	1
Haemoglobin-High G:G0(BL) to M(PBL) n=10,11,27,27	0	0	1	0

Lymphocytes–Low G:G0(BL) to G0(PBL) n=7,9,21,22	6	7	11	11
Lymphocytes–Low G:G0(BL) to G1(PBL) n=7,9,21,22	0	0	2	4
Lymphocytes–Low G:G0(BL) to G2(PBL) n=7,9,21,22	0	2	4	6
Lymphocytes–Low G:G0(BL) to G3(PBL) n=7,9,21,22	1	0	3	1
Lymphocytes–Low G:G0(BL) to M (PBL) n=7,9,21,22	0	0	1	0
Lymphocytes–Low G:G1(BL) to G0(PBL) n=0,1,2,1	99999	0	0	1
Lymphocytes–Low G:G1 (BL) to G2 (PBL) n=0,1,2,1	99999	1	1	0
Lymphocytes–Low G:G1(BL) to G3(PBL)n=0,1,2,1	99999	0	1	0
Lymphocytes–Low G:G2(BL) to G0(PBL) n=2,0,3,4	0	99999	1	0
Lymphocytes–Low G:G2(BL) to G2(PBL) n=2,0,3,4	1	99999	1	2
Lymphocytes–Low G:G2(BL) to G3(PBL) n=2,0,3,4	1	99999	1	2
Lymphocytes–Low G:G3(BL) to G0(PBL) n=1,1,1,0	0	0	1	99999
Lymphocytes–Low G:G3(BL) to G2(PBL) n=1,1,1,0	0	1	0	99999
Lymphocytes–Low G:G3(BL) to G3(PBL) n=1,1,1,0	1	0	0	99999
Lymphocytes-High: G0(BL) to G0(PBL) n=10,11,27,27	9	11	25	26
Lymphocytes-High: G0(BL) to G2(PBL) n=10,11,27,27	1	0	1	1
Lymphocytes-High: G0(BL) to M(PBL) n=10,11,27,27	0	0	1	0
Neutrophils-Low G: G0(BL) to G0(PBL) n=10,11,25,27	9	11	23	26
Neutrophils-Low G: G0(BL) to G1(PBL) n=10,11,25,27	0	0	1	1
Neutrophils-Low G: G0(BL) to G2(PBL) n=10,11,25,27	1	0	0	0
Neutrophils-Low G: G0(BL) to M(PBL) n=10,11,25,27	0	0	1	0
Neutrophils-Low G: G1(BL) to G0(PBL) n=0,0,2,0	99999	99999	1	99999
Neutrophils-Low G: G1(BL) to G3(PBL) n=0,0,2,0	99999	99999	1	99999
Platelet count-Low G:G0(BL)toG0(PBL)n=10,10,26,26	8	9	21	22
Platelet count-Low G:G0(BL)toG1(PBL)n=10,10,26,26	2	1	3	4
Platelet count-Low G:G0(BL)toM(PBL)n=10,10,26,26	0	0	2	0
Platelet count-Low G: G1(BL) to G0(PBL) n=0,1,1,1	99999	1	0	0
Platelet count-Low G: G1(BL) to G1(PBL) n=0,1,1,1	99999	0	1	1
WBC-Low: G0(BL) to G0(PBL) n=10,11,26,26	9	11	21	24
WBC-Low: G0(BL) to G1(PBL) n=10,11,26,26	0	0	2	0
WBC-Low: G0(BL) to G2(PBL) n=10,11,26,26	1	0	1	2

WBC-Low: G0(BL) to G4(PBL) n=10,11,26,26	0	0	1	0
WBC-Low: G0(BL) to M(PBL) n=10,11,26,26	0	0	1	0
WBC-Low: G1(BL) to G1(PBL) n=0,0,1,1	99999	99999	1	0
WBC-Low: G1(BL) to G2(PBL) n=0,0,1,1	99999	99999	0	1
WBC-High: G0(BL) to G0(PBL) n=10,11,27,27	10	11	26	27
WBC-High: G0(BL) to M(PBL) n=10,11,27,27	0	0	1	0
aPTT-High: G0(BL) to G0(PBL) n=10,10,24,24	6	8	16	17
aPTT-High: G0(BL) to G1(PBL) n=10,10,24,24	3	2	6	6
aPTT-High: G0(BL) to G2(PBL) n=10,10,24,24	1	0	2	1
aPTT-High: G1(BL) to G0(PBL) n=0,1,3,2	99999	0	0	1
aPTT-High: G1(BL) to G1(PBL) n=0,1,3,2	99999	1	1	1
aPTT-High: G1(BL) to G3(PBL) n=0,1,3,2	99999	0	1	0
aPTT-High: G1(BL) to M(PBL) n=0,1,3,2	99999	0	1	0
aPTT-High: M(BL) to G0(PBL) n=0,0,0,1	99999	99999	99999	1
INR-High: G0(BL) to G0(PBL) n=9,8,20,17	5	6	16	13
INR-High: G0(BL) to G1(PBL) n=9,8,20,17	4	2	4	4
INR-High: G1(BL) to G0(PBL) n=1,2,7,9	0	1	1	1
INR-High: G1(BL) to G1(PBL) n=1,2,7,9	1	1	5	8
INR-High: G1(BL) to M(PBL) n=1,2,7,9	0	0	1	0
INR-High: G2(BL) to G2(PBL) n=0,1,0,0	99999	1	99999	99999
INR-High: M(BL) to G0(PBL) n=0,0,0,1	99999	99999	99999	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift From Baseline in Laboratory Parameter Values Based on Normal Range: Haematology and Coagulation

End point title	Number of Subjects With Shift From Baseline in Laboratory Parameter Values Based on Normal Range: Haematology and Coagulation

End point description:

Haematology parameters: Basophils, Eosinophils, Haematocrit, Monocytes, Red blood cells(RBC). Coagulation parameters: Prothrombin Time(PT). Laboratory values were as per laboratory normal ranges. Values above range were reported as high and values below range as low. Laboratory parameters were graded based on laboratory normal ranges as low, normal, high and missing are reported in this endpoint. Categories with at least 1 non-zero data values are reported. Safety set included of all subjects who received at least 1 dose of study drug. Here "n": subjects evaluable for this endpoint for specified rows. Baseline=BL, Postbaseline=PBL. '99999' signifies data not available as none of the subjects were evaluable for specified categories.

End point type	Secondary

End point timeframe:

Phase 1b: Baseline up to 30 days after last dose (maximum up to 9 months approximately), Phase 2: Baseline up to 30 days after last dose (maximum up to 26 months approximately)

End point values	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Binimetinib	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	27	27
Units: Subjects				
Basophils: Normal(BL)to Low(PBL)n=10,11,27,27	0	0	1	0
Basophils: Normal(BL) to Normal(PBL) n=10,11,27,27	10	11	25	27
Basophils: Normal(BL) to Missing(PBL)n=10,11,27,27	0	0	1	0
Eosinophils: Normal(BL) to Low(PBL) n=9,11,27,27	0	0	0	1
Eosinophils: Normal(BL)to Normal(PBL)n=9,11,27,27	7	11	25	20
Eosinophils: Normal(BL) to High(PBL) n=9,11,27,27	2	0	1	6
Eosinophils:Normal(BL) to Missing(PBL)n=9,11,27,27	0	0	1	0
Eosinophils: High(BL) to Normal(PBL) n=1,0,0,0	1	99999	99999	99999
Haematocrit: Low(BL) to Low(PBL) n=2,2,10,9	2	1	8	9
Haematocrit: Low(BL) to Normal(PBL) n=2,2,10,9	0	1	1	0
Haematocrit: Low(BL) to Missing(PBL) n=2,2,10,9	0	0	1	0
Haematocrit: Normal(BL) to Low(PBL) n=8,9,17,18	5	4	13	12
Haematocrit: Normal(BL) to Normal(PBL) n=8,9,17,18	3	4	4	6
Haematocrit:Normal(BL) to High&Low(PBL)n=8,9,17,18	0	1	0	0
Monocytes: Normal(BL) to Low(PBL) n=10,11,27,26	1	0	1	0
Monocytes: Normal(BL) to Normal(PBL) n=10,11,27,26	9	7	19	20
Monocytes: Normal(BL) to High(PBL) n=10,11,27,26	0	4	6	6
Monocytes: Normal(BL)to Missing(PBL)n=10,11,27,26	0	0	1	0
Monocytes: High(BL) to Normal(PBL) n=0,0,0,1	99999	99999	99999	1
RBC: Low(BL) to Low(PBL) n=1,2,14,7	1	1	13	6
RBC: Low(BL) to Normal(PBL) n=1,2,14,7	0	1	1	1
RBC: Normal(BL) to Low(PBL) n=8,9,13,19	6	5	8	10
RBC: Normal(BL) to Normal(PBL) n=8,9,13,19	2	4	3	9
RBC: Normal(BL) to High(PBL) n=8,9,13,19	0	0	1	0
RBC: Normal(BL) to Missing(PBL) n=8,9,13,19	0	0	1	0
RBC: High(BL) to Low(PBL) n=1,0,0,1	0	99999	99999	1

RBC: High(BL) to Normal(PBL) n=1,0,0,1	1	99999	99999	0
PT: Normal(BL) to Normal(PBL) n=7,7,19,17	3	3	8	8
PT: Normal(BL) to High(PBL) n=7,7,19,17	4	4	11	9
PT: High (BL) to Normal(PBL) n=3,4,8,9	0	1	0	0
PT: High(BL) to High(PBL) n=3,4,8,9	3	3	7	9
PT: High(BL) to Missing(PBL) n=3,4,8,9	0	0	1	0
PT: Missing(BL) to High(PBL) n=0,0,0,1	99999	99999	99999	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift From Baseline in Laboratory Parameter Values Based on CTCAE v4.03: Chemistry

End point title	Number of Subjects With Shift From Baseline in Laboratory Parameter Values Based on CTCAE v4.03: Chemistry

End point description:

Abnormalities: Albumin-graded low(L), Alkaline phosphatase(ALP)-graded high(H), Alanine aminotransferase(ALT)-H, Aspartate aminotransferase(AST)-H, Bilirubin-H, Amylase-H, Creatinine-H, Corrected calcium-H, Creatine Kinase-H, Glucose-H, Glucose-L, Lipase-H, Magnesium-H, Magnesium-L, Potassium-H, Potassium-L, Sodium-H and Sodium-L. Abnormalities graded by CTCAE v4.03 G1=mild;G2=moderate;G 3/4=severe/life-threatening. A G0 was assigned for all non-missing values not graded as 1 or higher. If value graded >=1 but falls within normal range, grade was reset to 0. Categories with at least 1 non-zero data values are reported. Safety set-all subjects received at least 1 dose of study drug. Here "n"- subjects evaluable for this endpoint for specified rows. Baseline=BL, Postbaseline=PBL, Missing=M. 99999=data not available as none of the subjects were evaluable for

End point type	Secondary

End point timeframe:

Phase 1b: Baseline up to 30 days after last dose (maximum up to 9 months approximately), Phase 2: Baseline up to 30 days after last dose (maximum up to 26 months approximately)

End point values	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Binimetinib	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	27	27
Units: Subjects				
ALT-High: G0(BL) to G0(PBL) n=8,10,20,21	5	5	12	12
ALT-High: G0(BL) to G1(PBL) n=8,10,20,21	3	5	7	5
ALT-High: G0(BL) to G2(PBL) n=8,10,20,21	0	0	1	1
ALT-High: G0(BL) to G3(PBL) n=8,10,20,21	0	0	0	3
ALT-High: G1(BL) to G0(PBL) n=1,1,5,5	0	0	1	0
ALT-High: G1(BL) to G1(PBL) n=1,1,5,5	1	1	3	2
ALT-High: G1(BL) to G2(PBL) n=1,1,5,5	0	0	1	2
ALT-High: G1(BL) to G3(PBL) n=1,1,5,5	0	0	0	1

ALT-High: G2(BL) to G2(PBL) n=1,0,1,1	1	99999	1	0
ALT-High: G2(BL) to G3(PBL) n=1,0,1,1	0	99999	0	1
ALT-High: G3(BL) to Missing(PBL) n=0,0,1,0	99999	99999	1	99999
AST-High: G0(BL) to G0(PBL) n=8,7,21,22	3	2	8	5
AST-High: G0(BL) to G1(PBL) n=8,7,21,22	5	4	11	13
AST-High: G0(BL) to G2(PBL) n=8,7,21,22	0	1	2	2
AST-High: G0(BL) to G3(PBL) n=8,7,21,22	0	0	0	2
AST-High: G1(BL) to G1(PBL) n=2,4,5,5	2	4	3	1
AST-High: G1(BL) to G2(PBL) n=2,4,5,5	0	0	1	3
AST-High: G1(BL) to G3(PBL) n=2,4,5,5	0	0	1	1
AST-High: G2(BL) to Missing(PBL) n=0,0,1,0	99999	99999	1	99999
Albumin-Low: G0(BL) to G0(PBL) n=10,8,25,26	4	2	8	8
Albumin-Low: G0(BL) to G1(PBL) n=10,8,25,26	3	2	9	11
Albumin-Low: G0(BL) to G2(PBL) n=10,8,25,26	3	4	7	6
Albumin-Low: G0(BL) to G3(PBL) n=10,8,25,26	0	0	0	1
Albumin-Low: G0(BL) to Missing(PBL) n=10,8,25,26	0	0	1	0
Albumin-Low: G1(BL) to G1(PBL) n=0,2,2,1	99999	0	0	1
Albumin-Low: G1(BL) to G2(PBL) n=0,2,2,1	99999	2	2	0
Albumin-Low: G2(BL) to G2(PBL) n=0,1,0,0	99999	1	99999	99999
ALP-High: G0(BL) to G0(PBL) n=5,4,15,12	2	2	7	6
ALP-High: G0(BL) to G1(PBL) n=5,4,15,12	3	1	8	5
ALP-High: G0(BL) to G2(PBL) n=5,4,15,12	0	1	0	1
ALP-High: G1(BL) to G1(PBL) n=4,4,9,11	1	0	5	7
ALP-High: G1(BL) to G2(PBL) n=4,4,9,11	2	4	3	3
ALP-High: G1(BL) to G3(PBL) n=4,4,9,11	1	0	1	1
ALP-High: G2(BL) to G2(PBL) n=1,1,2,2	0	1	0	0
ALP-High: G2(BL) to G3(PBL) n=1,1,2,2	1	0	2	2
ALP-High: G3(BL) to G3(PBL) n=0,2,1,2	99999	2	0	2
ALP-High: G3(BL) to Missing(PBL) n=0,2,1,2	99999	0	1	0
Amylase-High: G0(Bl) to G0(PBL) n=9,11,27,26	8	7	18	20
Amylase-High: G0(BL) to G1(PBL) n=9,11,27,26	1	2	5	2
Amylase-High: G0(BL) to G2(PBL) n=9,11,27,26	0	0	1	2
Amylase-High: G0(BL) to G3(PBL) n=9,11,27,26	0	1	2	2
Amylase-High: G0(BL) to Missing(PBL) n=9,11,27,26	0	1	1	0

Amylase-High: G1(BL) to G2(PBL) n=1,0,0,0	1	99999	99999	99999
Amylase-High: G2(BL) to G4(PBL) n=0,0,0,1	99999	99999	99999	1
Bilirubin-High: G0(BL) to G0(PBL) n=10,10,26,27	10	9	25	24
Bilirubin-High: G0(BL) to G1(PBL) n=10,10,26,27	0	0	1	2
Bilirubin-High: G0(BL) to G2(PBL) n=10,10,26,27	0	1	0	1
Bilirubin-High: G1(BL) to G2(PBL) n=0,1,0,0	99999	1	99999	99999
Bilirubin-High: G4(BL) to Missing(PBL) n=0,0,1,0	99999	99999	1	99999
Corrected calcium-Low:G0(BL)toG0(PBL)n=10,11,27,26	7	11	24	25
Corrected calcium-Low:G0(BL)toG1(PBL)n=10,11,27,26	3	0	2	1
Corrected calcium-Low: G0(BL)toM(PBL)n=10,11,27,26	0	0	1	0
Corrected calcium-Low:G1(BL)to G0(PBL)n=0,0,0,1	99999	99999	99999	1
Correctedcalcium-High:G0(BL)toG0(PBL)n=10,11,27,26	10	11	25	25
Correctedcalcium-High:G0(BL)toG1(PBL)n=10,11,27,26	0	0	1	1
Correctedcalcium-High: G0(BL)toM(PBL)n=10,11,27,26	0	0	1	0
Corrected calcium-High:G1(BL)toG0(PBL)n=0,0,0,1	99999	99999	99999	1
Creatine kinase-High: G0(BL)toG0(PBL)n=9,10,27,23	1	3	3	7
Creatine kinase-High:G0(BL)toG1(PBL)n=9,10,27,23	3	4	11	7
Creatine kinase-High:G0(BL)toG2(PBL)n=9,10,27,23	4	2	6	8
Creatine kinase-High: G0(BL)toG3(PBL)n=9,10,27,23	1	1	5	1
Creatine kinase-High: G0(BL)toG4(PBL)n=9,10,27,23	0	0	1	0
Creatine kinase-High: G0(BL)toM(PBL)n=9,10,27,23	0	0	1	0
Creatine kinase-High:G1(BL)toG2(PBL)n=1,1,0,3	0	1	99999	1
Creatine kinase-High:G1(BL)toG3(PBL)n=1,1,0,3	1	0	99999	1
Creatine kinase-High: G1(BL)toG4(PBL)n=1,1,0,3	0	0	99999	1
Creatine kinase-High: M(BL)toG1(PBL)n=0,0,0,1	99999	99999	99999	1
Creatinine-High: G0(BL) to G0(PBL) n=10,11,27,27	1	2	6	7
Creatinine-High: G0(BL) to G1(PBL) n=10,11,27,27	7	7	14	18
Creatinine-High: G0(BL) to G2(PBL) n=10,11,27,27	2	2	5	2
Creatinine-High: G0(BL) to G4(PBL) n=10,11,27,27	0	0	1	0
Creatinine-High: G0(BL) to M(PBL) n=10,11,27,27	0	0	1	0
Glucose-Low: G0(BL) to G0(PBL) n=10,11,26,26	10	10	23	26

Glucose-Low: G0(BL) to G1(PBL) n=10,11,26,26	0	1	1	0
Glucose-Low: G0(BL) to G2(PBL) n=10,11,26,26	0	0	1	0
Glucose-Low: G0(BL) to M(PBL) n=10,11,26,26	0	0	1	0
Glucose-Low: G1(BL) to G0(PBL) n=0,0,1,1	99999	99999	0	1
Glucose-Low: G1(BL) to G1(PBL) n=0,0,1,1	99999	99999	1	0
Glucose-High: G0(BL) to G0(PBL) n=9,10,24,21	7	6	18	14
Glucose-High: G0(BL) to G1(PBL) n=9,10,24,21	0	1	1	1
Glucose-High: G0(BL) to G2(PBL) n=9,10,24,21	1	1	0	1
Glucose-High: G0(BL) to M(PBL) n=9,10,24,21	1	2	5	5
Glucose-High: G1(BL) to G0(PBL) n=0,0,1,1	99999	99999	1	0
Glucose-High: G1(BL) to G2(PBL) n=0,0,1,1	99999	99999	0	1
Glucose-High: G3(BL) to G2(PBL) n=0,0,1,2	99999	99999	1	0
Glucose-High: G3(BL) to G3(PBL) n=0,0,1,2	99999	99999	0	1
Glucose-High: G3(BL) to M(PBL) n=0,0,1,2	99999	99999	0	1
Glucose-High: M(BL) to G0(PBL) n=1,1,1,3	0	0	0	1
Glucose-High: M(BL) to G3(PBL) n=1,1,1,3	0	0	1	0
Glucose-High: M(BL) to M(PBL) n=1,1,1,3	1	1	0	2
Lipase-High: G0(BL) to G0(PBL) n=9,10,25,23	5	6	17	15
Lipase-High: G0(BL) to G1(PBL) n=9,10,25,23	2	2	2	4
Lipase-High: G0(BL) to G2(PBL) n=9,10,25,23	1	1	1	0
Lipase-High: G0(BL) to G3(PBL) n=9,10,25,23	1	0	4	3
Lipase-High: G0(BL) to G4(PBL) n=9,10,25,23	0	0	0	1
Lipase-High: G0(BL) to M(PBL) n=9,10,25,23	0	1	1	0
Lipase-High: G1(BL) to G0(PBL) n=1,1,2,3	1	0	1	0
Lipase-High: G1(BL) to G1(PBL) n=1,1,2,3	0	1	1	2
Lipase-High: G1(BL) to G3(PBL) n=1,1,2,3	0	0	0	1
Lipase-High: G4(BL) to G4(PBL) n=0,0,0,1	99999	99999	99999	1
Magnesium-Low: G0(BL) to G0(PBL) n=9,11,26,27	8	10	22	24
Magnesium-Low: G0(BL) to G1(PBL) n=9,11,26,27	1	1	3	2
Magnesium-Low: G0(BL) to G2(PBL) n=9,11,26,27	0	0	0	1
Magnesium-Low: G0(BL) to M(PBL) n=9,11,26,27	0	0	1	0

Magnesium-Low: G1(BL) to G2(PBL) n=1,0,0,0	1	99999	99999	99999
Magnesium-Low: G2(BL) toG3(PBL) n=0,0,1,0	99999	99999	1	99999
Magnesium-High: G0(BL) to G0(PBL) n=10,11,27,27	10	11	26	27
Magnesium-High: G0(BL) to M(PBL) n=10,11,27,27	0	0	1	0
Potassium-Low: G0(BL) to G0(PBL) n=10,11,26,27	7	9	20	23
Potassium-Low: G0(BL) to G1(PBL) n=10,11,26,27	3	2	3	4
Potassium-Low: G0(BL) to G3(PBL) n=10,11,26,27	0	0	1	0
Potassium-Low: G0(BL) to G4(PBL) n=10,11,26,27	0	0	1	0
Potassium-Low: G0(BL) to M(PBBL) n=10,11,26,27	0	0	1	0
Potassium-Low: G3(BL) to G3 (PBL) n=0,0,1,0	99999	99999	1	99999
Potassium-High: G0(BL) to G0(PBL) n=10,11,26,27	9	10	23	23
Potassium-High: G0(BL) toG1(PBL) n=10,11,26,27	1	1	2	4
Potassium-High: G0(BL) to M(PBL) n=10,11,26,27	0	0	1	0
Potassium-High: G1(BL) to G0(PBL) n=0,0,1,0	99999	99999	1	99999
Sodium-Low: G0(BL) to G0(PBL) n=10,10,25,27	8	7	19	23
Sodium-Low: G0(BL) to G1(PBL) n=10,10,25,27	1	3	3	1
Sodium-Low: G0(BL) to G3(PBL) n=10,10,25,27	0	0	1	2
Sodium-Low: G0(BL) to G4(PBL) n=10,10,25,27	0	0	2	1
Sodium-Low: G1(BL) to G1(PBL) n=0,0,2,0	99999	99999	1	99999
Sodium-Low: G1(BL) to M(PBL) n=0,0,2,0	99999	99999	1	99999
Sodium-Low: G3(BL) to G3(PBL) n=0,1,0,0	99999	1	99999	99999
Sodium-High: G0(BL) to G0(PBL) n=10,11,27,27	10	11	23	22
Sodium-High: G0(BL) to G1(PBL) n=10,11,27,27	0	0	3	5
Sodium-High: G0(BL) to M(PBL) n=10,11,27,27	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift From Baseline in Laboratory Parameter Values Based on Normal Range: Chemistry and Thyroid Function

End point title	Number of Subjects With Shift From Baseline in Laboratory Parameter Values Based on Normal Range: Chemistry and Thyroid Function

End point description:

Chemistry laboratory parameters:Blood urea nitrogen (BUN), Protein, Chloride, Cancer antigen19-9 (CA19-9), Brain natriuretic peptide(BNP), Bicarbonate, Carcinoembryonic antigen(CEA), Lactate dehydrogenase(LDH), Uric acid, Troponin I. Thyroid panel laboratory parameters: Thyroid-stimulating hormone(TSH), Free triiodothyronine(T3), Free thyroxine(T4). Laboratory values were as per laboratory normal ranges. Values above range were reported as high and values below range as low. Shift in chemistry and thyroid panel severity from baseline grade low, normal, high and missing to the post baseline grades as low, normal, high and missing are reported in this endpoint. Categories with at least 1 non-zero data values are reported. Safety set:all subjects who received at least 1 dose of study drug. 'n'=subjects evaluable for this endpoint for specified rows. Baseline=BL, Postbaseline=PBL, Missing=M. '99999'=data not available as none of the subjects were evaluable for specified categories.

End point type	Secondary

End point timeframe:

Phase 1b: Baseline up to 30 days after last dose (maximum up to 9 months approximately), Phase 2: Baseline up to 30 days after last dose (maximum up to 26 months approximately)

End point values	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Binimetinib	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	27	27
Units: Subjects				
BNP: Normal(BL) to Normal(PBL) n=9,9,27,25	8	6	24	22
BNP: Normal(BL) to High(PBL) n=9,9,27,25	1	3	2	3
BNP: Normal(BL) to Missing(PBL) n=9,9,27,25	0	0	1	0
BNP: High(BL) to Normal(PBL) n=1,2,0,2	0	2	99999	0
BNP: High(BL) to High(PBL) n=1,2,0,2	1	0	99999	2
BUN: Normal(BL) to Normal(PBL) n=7,9,25,21	4	3	15	14
BUN: Normal(BL) to High(PBL) n=7,9,25,21	3	5	9	7
BUN: Normal(BL) to Missing(PBL) n=7,9,25,21	0	1	1	0
BUN: High(BL) to Normal(PBL) n=3,2,2,6	0	0	2	3
BUN: High(BL) to High(PBL) n=3,2,2,6	3	2	0	3
Bicarbonate: Low(BL) to Normal(PBL) n=0,2,1,3	99999	1	0	3
Bicarbonate: Low(BL) to High(PBL) n=0,2,1,3	99999	1	1	0
Bicarbonate: Normal(BL) to Low(PBL) n=10,9,26,24	2	1	6	9
Bicarbonate:Normal(BL)to Normal(PBL)n=10,9,26,24	7	6	18	11
Bicarbonate: Normal(BL) to High(PBL) n=10,9,26,24	1	2	1	3
Bicarbonate:Normal(BL)toHigh&Low(PBL)n=10,9,26,24	0	0	0	1
Bicarbonate:Normal(BL)to Missing(PBL)n=10,9,26,24	0	0	1	0
CA19-9: Normal(BL) to Normal(PBL) n=3,4,8,9	3	3	6	7

CA19-9: Normal(BL) to High(PBL) n=3,4,8,9	0	0	2	1
CA19-9: Normal(BL) to Missing(PBL) n=3,4,8,9	0	1	0	1
CA19-9: High(BL) to Normal(PBL) n=7,7,19,18	0	0	1	1
CA19-9: High(BL) to High(PBL) n=7,7,19,18	7	6	16	16
CA19-9: High(BL) to Missing(PBL) n=7,7,19,18	0	1	2	1
CEA: Normal(BL) to Normal(PBL) n=1,0,3,6	1	99999	1	3
CEA: Normal(BL) to High(PBL) n=1,0,3,6	0	99999	2	2
CEA: Normal(BL) to Missing(PBL) n=1,0,3,6	0	99999	0	1
CEA: High(BL) to Normal(PBL) n=9,11,24,21	0	0	1	0
CEA: High(BL) to High(PBL) n=9,11,24,21	9	9	20	20
CEA: High(BL) to Missing(PBL) n=9,11,24,21	0	2	3	1
Chloride: Low(BL) to Low(PBL) n=0,1,2,1	99999	1	1	1
Chloride: Low(BL) to Missing(PBL) n=0,1,2,1	99999	0	1	0
Chloride: Normal(BL) to Low(PBL) n=10,10,25,26	2	2	8	3
Chloride: Normal(BL) to Normal(PBL) n=10,10,25,26	8	7	15	22
Chloride: Normal(BL) to High(PBL) n=10,10,25,26	0	0	2	1
Chloride:Normal(BL)to High&Low(PBL)n=10,10,25,26	0	1	0	0
T3: Low(BL) to Low(PBL) n=0,0,1,2	99999	99999	0	1
T3: Low(BL) to Missing(PBL) n=0,0,1,2	99999	99999	1	1
T3: Normal(BL) to Low(PBL) n=10,11,26,23	3	5	8	7
T3: Normal(BL) to Normal(PBL) n=10,11,26,23	7	5	15	15
T3:Normal(BL) to High&Low(PBL)n=10,11,26,23	0	0	1	0
T3: Normal(BL) to Missing(PBL) n=10,11,26,23	0	1	2	1
T3: High(BL) to High(PBL) n=0,0,0,2	99999	99999	99999	2
T4: Low(BL) to Low(PBL) n=0,1,0,1	99999	0	99999	1
T4: Low(BL) to Normal(PBL) n=0,1,0,1	99999	1	99999	0
T4: Normal(BL) to Low(PBL) n=10,10,26,24	0	1	2	3
T4: Normal(BL) to Normal(PBL)n=10,10,26,24	10	8	17	17
T4: Normal(BL) to High(PBL) n=10,10,26,24	0	0	3	1
T4:Normal(BL)to High&Low(PBL)n=10,10,26,24	0	0	1	1
T4: Normal(BL) to Missing(PBL) n=10,10,26,24	0	1	3	2
T4: High(BL) to Low(PBL) n=0,0,1,2	99999	99999	0	1
T4: High(BL) to Nomal(PBL) n=0,0,1,2	99999	99999	1	1
LDH: Low(BL) to Low(PBL) n=1,0,0,0	1	99999	99999	99999

LDH: Normal(BL) to Normal(PBL) n=6,5,20,15	1	1	6	5
LDH: Normal(BL) to High(PBL) n=6,5,20,15	5	4	14	10
LDH: High(BL) to Normal(PBL) n=3,6,7,12	0	0	0	1
LDH: High(BL) to High(PBL) n=3,6,7,12	3	6	6	11
LDH: High(BL) to Missing(PBL) n=3,6,7,12	0	0	1	0
Protein: Low(BL) to Low(PBL) n=0,1,0,0	99999	1	99999	99999
Protein: Normal(BL) to Low(PBL) n=10,10,27,27	5	6	11	11
Protein: Normal(BL) to Normal(PBL) n=10,10,27,27	5	4	12	14
Protein: Normal(BL) to High(PBL) n=10,10,27,27	0	0	0	2
Protein:Normal(BL)to High&Low(PBL)n=10,10,27,27	0	0	3	0
Protein: Normal(BL) to Missing(PBL) n=10,10,27,27	0	0	1	0
TSH: Low(BL) to Low(PBL) n=0,0,0,1	99999	99999	99999	1
TSH: Normal(BL) to Low(PBL) n=9,7,24,26	0	0	2	3
TSH: Normal(BL) to Normal(PBL) n=9,7,24,26	8	7	14	20
TSH: Normal(BL) to High(PBL) n=9,7,24,26	1	0	3	1
TSH:Normal(BL)to High&Low(PBL)n=9,7,24,26	0	0	2	0
TSH: Normal(BL) to Missing(PBL) n=9,7,24,26	0	0	3	2
TSH: High(BL) to Normal(PBL) n=1,4,3,0	0	2	2	99999
TSH: High(BL) to High(PBL) n=1,4,3,0	1	1	1	99999
TSH: High(BL) to Missing(PBL) n=1,4,3,0	0	1	0	99999
Troponin I: Normal(BL) to Normal(PBL)n=0,2,26,26	99999	2	11	10
Troponin I: Normal(BL) to High(PBL)n=0,2,26,26	99999	0	1	2
Troponin I: Normal(BL) to Missing(PBL) n=0,2,26,26	99999	0	14	14
Troponin I: Missing(BL)to Normal(PBL)n=5,3,0,1	4	3	99999	1
Troponin I: Missing(BL) to High(PBL) n=5,3,0,1	1	0	99999	0
Uric acid: Low(BL) to Low(PBL) n=0,1,1,3	99999	0	0	2
Uric acid: Low(BL) to Normal(PBL) n=0,1,1,3	99999	1	0	1
Uric acid: Low(BL) to Missing(PBL) n=0,1,1,3	99999	0	1	0
Uric acid: Normal(BL) to Low(PBL) n=9,9,23,21	1	2	4	4
Uric acid: Normal(BL) to Normal(PBL)n=9,9,23,21	8	5	15	16
Uric acid: Normal(BL) to High(PBL) n=9,9,23,21	0	2	4	1
Uric acid: High(BL) to Normal(PBL) n=1,1,3,3	0	0	1	0

Uric acid: High(BL) to High(PBL) n=1,1,3,3	1	1	2	3

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormal Hepatic Laboratory Values

End point title	Number of Subjects With Abnormal Hepatic Laboratory Values

End point description:

Criteria for abnormal hepatic laboratory parameters: Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT): >3* upper limit of normal (ULN), >5*ULN, >8*ULN, >10*ULN, >20*ULN; Total bilirubin (TBL) >1.5*ULN, >2*ULN; Alkaline phosphatase (ALP) >2*ULN, >3*ULN. Categories with at least 1 non-zero data values are reported. Safety set: all subjects who received at least 1 dose of study drug. 'n'=subjects evaluable for this endpoint for specified rows.

End point type	Secondary

End point timeframe:

Phase 1b: Baseline up to 30 days after last dose (maximum up to 9 months approximately), Phase 2: Baseline up to 30 days after last dose (maximum up to 26 months approximately)

End point values	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Binimetinib	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	27	27
Units: Subjects				
ALT: >3 ULN n=9,11,25,26	0	0	2	7
ALT: >5 ULN n=10,11,26,27	0	0	0	5
ALT: >8 ULN n=10,11,26,27	0	0	0	1
AST: >3 ULN n=10,11,26,27	0	1	4	8
AST: >5 ULN n=10,11,26,27	0	0	1	3
AST: >8 ULN n=10,11,26,27	0	0	1	1
ALT or AST: >3 ULN n=9,11,25,26	0	1	3	7
ALT or AST: >5 ULN n=10,11,26,27	0	0	1	4
ALT or AST: >8 ULN n=10,11,26,27	0	0	1	1
Total bilirubin: >1.5 ULN n=9,11,26,26	0	2	0	1
Alkaline phosphatase: >2 ULN n=8,6,22,22	3	3	4	8
Alkaline phosphatase: >3 ULN n=10,8,24,24	4	4	2	4

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration Versus Time Summary of Plasma Concentration of Binimetinib

End point title	Concentration Versus Time Summary of Plasma Concentration of Binimetinib

End point description:

The pharmacokinetic analysis set included of all subjects who received at least 1 dose of binimetinib and have at least 1 evaluable bioanalytical result. Here, 'n' signifies subjects evaluable for this endpoint for specified rows. '99999'= geometric mean and geometric coefficient of variation were not estimable as concentration was below the limit of quantification. '9999'=data not available as none of the subjects were evaluable for specified categories.

End point type	Secondary

End point timeframe:

1.5 hours post dose of binimetinib on Day 1, 15 of Cycle 1; pre dose of binimetinib on Day 15 of Cycle 1, 2, 3, 4, 5

End point values	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Binimetinib	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	26	27
Units: nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1: 1.5 hours post dose n=10,11,21,23	228 (± 152.2)	163 (± 129.6)	261 (± 90.9)	217 (± 134.5)
Cycle 1 Day 15: pre dose n=4,5,12,8	135 (± 60.9)	125 (± 103.9)	77 (± 141.2)	81.8 (± 143.6)
Cycle 1 Day 15: 1.5 hours post dose n=4,8,15,18	542 (± 57.6)	414 (± 24.5)	294 (± 84.4)	324 (± 83.3)
Cycle 2 Day 15: pre dose n=4,2,7,7	108 (± 52.9)	99999 (± 99999)	88.5 (± 111.3)	120 (± 77.7)
Cycle 3 Day 15: pre dose n=3,2,1,3	140 (± 42.0)	99999 (± 99999)	99999 (± 99999)	89.2 (± 183.4)
Cycle 4 Day 15: pre dose n=2,1,1,1	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Cycle 5 Day 15: pre dose n=1,0,1,1	99999 (± 99999)	9999 (± 9999)	99999 (± 99999)	99999 (± 99999)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-Cause Mortality:Treatment start upto 150days(D) after last dose(Phase1b:max upto 13months[m] approx,Phase2: max upto 30m approx);TEAEs (serious/other AEs):Treatment start upto 30D after last dose(Phase1b:max upto 9m approx.;Phase2:max upto 26m approx)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event. Safety set was evaluated. Both TEAE and treatment-related AEs were monitored.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Phase 1b: Nivolumab+Binimetinib

Reporting group description:

Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received binimetinib at a starting dose of 45 mg tablet orally BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle. Binimetinib dose modification to intermitted dosing (3 weeks on treatment and 1 week off treatment) with 45 mg dose or dose reduction to 30 mg BID or 30 mg intermittent dosing based on investigator’s decision as per its tolerability among subjects. Subjects then followed up for safety for around 150 days.

Reporting group title	Phase 1b: Nivolumab+Ipilimumab+Binimetinib

Reporting group description:

Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received binimetinib at a starting dose of 45 mg tablet BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle. Ipilimumab was administered at the dose of 1 mg/kg IV every 8 weeks after completion of nivolumab infusion. Binimetinib dose modification to intermitted dosing (3 weeks on treatment and 1 week off treatment) with 45 mg dose or dose reduction to 30 mg BID or 30 mg intermittent dosing based on investigator’s decision as per its tolerability among subjects. Subjects then followed up for safety for around 150 days.

Reporting group title	Phase 2: Nivolumab+Ipilimumab+Binimetinib

Reporting group description:

Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received 45 mg binimetinib tablet orally BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle. Ipilimumab was administered at the dose of 1 mg/kg IV every 8 weeks after completion of nivolumab infusion until disease progression, unacceptable toxicity, withdrawal of informal consent, initiation of subsequent anticancer therapy, lost to follow-up or death. Subjects then followed up for safety for around 150 days.

Reporting group title	Phase 2: Nivolumab+Binimetinib

Reporting group description:

Subjects with previously treated MSS metastatic colorectal cancer with RAS mutation received 45 mg binimetinib tablet orally BID along with 480 mg IV dose of nivolumab every 4 weeks in each 28 day treatment cycle, until disease progression, unacceptable toxicity, withdrawal of informal consent, initiation of subsequent anticancer therapy, lost to follow-up or death. Subjects then followed up for safety for around 150 days.

Serious adverse events	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	6 / 11 (54.55%)	11 / 27 (40.74%)

number of deaths (all causes)	8	8	21
number of deaths resulting from adverse events			
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (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			
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hip fracture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (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
Infusion related reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocarditis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (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
Pericardial effusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (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
Cardiac failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (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
Pleurisy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (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
Pulmonary oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)

occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (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
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (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
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (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
Nephritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (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 reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (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			
Pneumonia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (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

Candida infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infected seroma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (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 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (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

Serious adverse events	Phase 2: Nivolumab+Binimetinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 27 (44.44%)		
number of deaths (all causes)	20		
number of deaths resulting from adverse events			
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Localised oedema			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		

deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocarditis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			

subjects affected / exposed	2 / 27 (7.41%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pneumonitis				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleurisy				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				

Ataxia				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Intestinal obstruction				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				

subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephritis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin reaction			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myositis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal infection			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		

deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Candida infection				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Empyema				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infected seroma				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Klebsiella bacteraemia				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Periorbital cellulitis				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase 1b: Nivolumab+Binimetinib	Phase 1b: Nivolumab+Ipilimumab+Binimetinib	Phase 2: Nivolumab+Ipilimumab+Binimetinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	11 / 11 (100.00%)	27 / 27 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	4 / 27 (14.81%)
occurrences (all)	0	1	4
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Tumour associated fever			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Basal cell carcinoma			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 10 (40.00%)	6 / 11 (54.55%)	11 / 27 (40.74%)
occurrences (all)	7	8	20

Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	3 / 11 (27.27%)	14 / 27 (51.85%)
occurrences (all)	4	5	17
Oedema peripheral			
subjects affected / exposed	5 / 10 (50.00%)	5 / 11 (45.45%)	11 / 27 (40.74%)
occurrences (all)	7	8	19
Chills			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	4 / 27 (14.81%)
occurrences (all)	1	1	6
Asthenia			
subjects affected / exposed	3 / 10 (30.00%)	1 / 11 (9.09%)	9 / 27 (33.33%)
occurrences (all)	5	2	17
Face oedema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Localised oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	3
Influenza like illness			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Confusional state			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Scrotal oedema			

subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Pruritus genital			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Abdominal injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Skin abrasion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Laceration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Scratch			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 10 (50.00%)	3 / 11 (27.27%)	13 / 27 (48.15%)
occurrences (all)	19	13	40
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	5 / 27 (18.52%)
occurrences (all)	1	0	6
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	8 / 27 (29.63%)
occurrences (all)	0	2	23
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	3 / 11 (27.27%)	9 / 27 (33.33%)
occurrences (all)	0	3	21
Ejection fraction decreased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	7 / 27 (25.93%)
occurrences (all)	1	0	12
Amylase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	10
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	5
Lipase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	11
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Platelet count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Troponin I increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Troponin T increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	3
Electrocardiogram abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Intraocular pressure increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0

Cardiac disorders			
Ventricular hypokinesia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Cardiac failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 10 (20.00%)	3 / 11 (27.27%)	6 / 27 (22.22%)
occurrences (all)	3	3	6
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	4 / 11 (36.36%)	4 / 27 (14.81%)
occurrences (all)	0	6	8
Pneumonitis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	0 / 27 (0.00%)
occurrences (all)	0	4	0
Dysphonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	2 / 27 (7.41%)
occurrences (all)	0	1	7
Epistaxis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Rales			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Dyspnoea exertional			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Wheezing			

subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	4 / 27 (14.81%)
occurrences (all)	0	1	6
Leukopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 10 (10.00%)	2 / 11 (18.18%)	2 / 27 (7.41%)
occurrences (all)	1	2	2
Syncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Neuropathy peripheral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Periorbital oedema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Visual impairment			
subjects affected / exposed	2 / 10 (20.00%)	1 / 11 (9.09%)	3 / 27 (11.11%)
occurrences (all)	3	1	4
Eyelid oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)

occurrences (all)	0	0	2
Subretinal fluid			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Macular oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Eye oedema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Dry age-related macular degeneration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Photopsia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Retinopathy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Vitreous detachment			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 10 (60.00%)	4 / 11 (36.36%)	15 / 27 (55.56%)
occurrences (all)	21	7	36
Constipation			
subjects affected / exposed	2 / 10 (20.00%)	3 / 11 (27.27%)	6 / 27 (22.22%)
occurrences (all)	2	4	6
Vomiting			
subjects affected / exposed	2 / 10 (20.00%)	8 / 11 (72.73%)	10 / 27 (37.04%)
occurrences (all)	9	10	16

Nausea			
subjects affected / exposed	5 / 10 (50.00%)	2 / 11 (18.18%)	11 / 27 (40.74%)
occurrences (all)	8	3	12
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	5 / 27 (18.52%)
occurrences (all)	1	0	5
Dry mouth			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	5 / 27 (18.52%)
occurrences (all)	0	1	5
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 11 (18.18%)	3 / 27 (11.11%)
occurrences (all)	3	2	6
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	3 / 27 (11.11%)
occurrences (all)	0	1	3
Dyspepsia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	3 / 27 (11.11%)
occurrences (all)	1	1	3
Abdominal discomfort			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	2 / 27 (7.41%)
occurrences (all)	0	1	2
Ascites			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	5 / 27 (18.52%)
occurrences (all)	1	0	5
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	2 / 27 (7.41%)
occurrences (all)	0	1	2
Proctalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2

Pancreatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	3
Haemorrhoids			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Mesenteric arterial occlusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Glossitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Colitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	3	0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Small intestinal obstruction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Chromaturia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Renal colic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			

Dermatitis acneiform			
subjects affected / exposed	7 / 10 (70.00%)	6 / 11 (54.55%)	12 / 27 (44.44%)
occurrences (all)	15	15	25
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	3 / 11 (27.27%)	7 / 27 (25.93%)
occurrences (all)	0	4	9
Dry skin			
subjects affected / exposed	1 / 10 (10.00%)	2 / 11 (18.18%)	5 / 27 (18.52%)
occurrences (all)	1	2	6
Rash			
subjects affected / exposed	3 / 10 (30.00%)	1 / 11 (9.09%)	14 / 27 (51.85%)
occurrences (all)	5	4	32
Pruritus generalised			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	2 / 27 (7.41%)
occurrences (all)	0	1	2
Erythema			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	2 / 27 (7.41%)
occurrences (all)	3	1	2
Alopecia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Rash maculo-papular			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	1	6	0
Rash papular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Rash macular			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Rash pruritic			
subjects affected / exposed	2 / 10 (20.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0

Ecchymosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Hyperhidrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	19	1	0
Petechiae			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Exfoliative rash			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	3	0
Rash erythematous			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Skin fissures			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Skin reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Skin lesion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	4 / 27 (14.81%)
occurrences (all)	0	0	4
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Neck pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	2 / 27 (7.41%)
occurrences (all)	0	2	3
Muscular weakness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 10 (20.00%)	3 / 11 (27.27%)	6 / 27 (22.22%)
occurrences (all)	2	3	6
Dehydration			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	2	2	0
Hyperglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2

Hypomagnesaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	5
Hypokalaemia			
subjects affected / exposed	2 / 10 (20.00%)	1 / 11 (9.09%)	2 / 27 (7.41%)
occurrences (all)	5	1	2
Hypophosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	2 / 27 (7.41%)
occurrences (all)	0	6	4
Hypoalbuminaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Paronychia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	3 / 27 (11.11%)
occurrences (all)	1	1	4
Rash pustular			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	3 / 27 (11.11%)
occurrences (all)	1	1	6
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)

occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	6
Pneumonia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Phase 2: Nivolumab+Binimetinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	4		
Hypotension			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Tumour associated fever			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Basal cell carcinoma			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	11 / 27 (40.74%) 18		
Pyrexia subjects affected / exposed occurrences (all)	8 / 27 (29.63%) 19		
Oedema peripheral subjects affected / exposed occurrences (all)	8 / 27 (29.63%) 14		
Chills subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4		
Asthenia subjects affected / exposed occurrences (all)	7 / 27 (25.93%) 18		
Face oedema subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 5		
Localised oedema subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Influenza like illness subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Confusional state subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Insomnia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Reproductive system and breast disorders			

Benign prostatic hyperplasia subjects affected / exposed occurrences (all) Scrotal oedema subjects affected / exposed occurrences (all) Pruritus genital subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Abdominal injury subjects affected / exposed occurrences (all) Skin abrasion subjects affected / exposed occurrences (all) Laceration subjects affected / exposed occurrences (all) Scratch subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0		
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase	 14 / 27 (51.85%) 40 0 / 27 (0.00%) 0 2 / 27 (7.41%) 2		

increased				
subjects affected / exposed	2 / 27 (7.41%)			
occurrences (all)	3			
Ejection fraction decreased				
subjects affected / exposed	4 / 27 (14.81%)			
occurrences (all)	4			
Amylase increased				
subjects affected / exposed	3 / 27 (11.11%)			
occurrences (all)	3			
Blood bilirubin increased				
subjects affected / exposed	2 / 27 (7.41%)			
occurrences (all)	3			
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Lipase increased				
subjects affected / exposed	2 / 27 (7.41%)			
occurrences (all)	2			
Weight decreased				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Platelet count decreased				
subjects affected / exposed	2 / 27 (7.41%)			
occurrences (all)	2			
Troponin I increased				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Troponin T increased				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Electrocardiogram abnormal				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Prothrombin time prolonged				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			

Intraocular pressure increased			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Ventricular hypokinesia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Cardiac failure			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	11		
Dyspnoea			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	6		
Pneumonitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Dysphonia			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	4		
Productive cough			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Rales			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Dyspnoea exertional			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Nasal congestion			

subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 27 (25.93%)		
occurrences (all)	15		
Leukopenia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Thrombocytopenia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Neuropathy peripheral			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Eye disorders			
Periorbital oedema			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Visual impairment			
subjects affected / exposed	0 / 27 (0.00%)		

occurrences (all)	0		
Eyelid oedema			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Subretinal fluid			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Macular oedema			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Vision blurred			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Eye oedema			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Dry age-related macular degeneration			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Photopsia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Retinopathy			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Vitreous detachment			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 27 (48.15%)		
occurrences (all)	31		
Constipation			
subjects affected / exposed	9 / 27 (33.33%)		
occurrences (all)	10		

Vomiting				
subjects affected / exposed	7 / 27 (25.93%)			
occurrences (all)	7			
Nausea				
subjects affected / exposed	12 / 27 (44.44%)			
occurrences (all)	13			
Abdominal pain				
subjects affected / exposed	5 / 27 (18.52%)			
occurrences (all)	5			
Dry mouth				
subjects affected / exposed	3 / 27 (11.11%)			
occurrences (all)	3			
Stomatitis				
subjects affected / exposed	3 / 27 (11.11%)			
occurrences (all)	9			
Abdominal distension				
subjects affected / exposed	3 / 27 (11.11%)			
occurrences (all)	3			
Dyspepsia				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Abdominal discomfort				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Ascites				
subjects affected / exposed	4 / 27 (14.81%)			
occurrences (all)	6			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Abdominal pain upper				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Proctalgia				
subjects affected / exposed	2 / 27 (7.41%)			
occurrences (all)	2			

Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Pancreatitis subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Haemorrhoids subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Mesenteric arterial occlusion subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Glossitis subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Colitis subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Lower gastrointestinal haemorrhage subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Small intestinal obstruction subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Proteinuria subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Chromaturia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Renal colic subjects affected / exposed	0 / 27 (0.00%)		

occurrences (all)	0		

Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	13 / 27 (48.15%)		
occurrences (all)	22		
Pruritus			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	5		
Dry skin			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	8 / 27 (29.63%)		
occurrences (all)	13		
Pruritus generalised			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Alopecia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Rash maculo-papular			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Rash papular			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Rash macular			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	4		
Acne			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		

Rash pruritic				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Ecchymosis				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Dermatitis exfoliative generalised				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Hyperhidrosis				
subjects affected / exposed	2 / 27 (7.41%)			
occurrences (all)	2			
Dermatitis				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Petechiae				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Exfoliative rash				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Rash erythematous				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Skin fissures				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Skin reaction				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Skin lesion				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Skin hyperpigmentation				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			

Urticaria			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	11		
Myalgia			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Arthralgia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 27 (48.15%)		
occurrences (all)	13		
Dehydration			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		

Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Hypokalaemia subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 5		
Hypophosphataemia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3		
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Hyperuricaemia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Infections and infestations Paronychia subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 9		
Rash pustular subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 7		
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Conjunctivitis subjects affected / exposed	0 / 27 (0.00%)		

occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2018	(1) To add a 150-day safety follow-up assessment; (2) To remove visual field testing as part of the full ophthalmic examination; and (3) To state that visual field testing will only be performed when clinically indicated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported