Clinical trial results:
A Multistage, Phase II Study Evaluating the Safety and Efficacy of Cobimetinib Plus Paclitaxel, Cobimetinib Plus Atezolizumab Plus Paclitaxel, or Cobimetinib Plus Atezolizumab Plus Nab-Paclitaxel as First-Line Treatment for Patients With Metastatic Triple-Negative Breast Cancer

Summary

EudraCT number	2014-002230-32
Trial protocol	ES GB CZ BE FR LT LV IT
Global end of trial date	17 September 2021

Results information

Result version number	v6 (current)
This version publication date	01 April 2023
First version publication date	08 September 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	WO29479

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02322814
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.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	17 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to evaluate the safety and tolerability and estimate the efficacy of cobimetinib plus paclitaxel versus placebo plus paclitaxel in Cohort I, of cobimetinib plus atezolizumab plus paclitaxel in Cohort II, and of cobimetinib plus atezolizumab plus nab-paclitaxel in Cohort III in participants with metastatic or locally advanced, triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for metastatic breast cancer (MBC).

Protection of trial subjects:

All study subjects were required to read and sign and Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	Latvia: 18
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	169
EEA total number of subjects	97

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)	137
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study recruited participants with metastatic or locally advanced, triple-negative adenocarcinoma of the breast who had not received prior systemic therapy for metastatic breast cancer. Locally advanced disease must not have been amenable to resection with curative intent.

Pre-assignment

Screening details:

One participant from Cohort III never started any treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The run-in stage of Cohort I and all of Cohorts II and III were open label. The expansion (randomized) stage of Cohort I was double-blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort I: Safety Run-In

Arm description:

Participants received cobimetinib plus paclitaxel until 12 participants completed one cycle of study treatment (28 days).

Arm type	Experimental
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was administered at a dose of 80 milligrams per square meter (mg/m^2) by intravenous (IV) infusion on Day 1, Day 8, and Day 15 of each 28-day cycle according to prescribing information.

Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	Cotellic
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib was administered orally at a dose of 60 milligrams (mg) per day, once a day, on Day 3 through Day 23 of each 28-day treatment cycle.

Arm title	Cohort I: Cobimetinib, Paclitaxel

Arm description:

Participants received a combination of cobimetinib plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

Arm type	Experimental

Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	Cotellic
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib was administered orally at a dose of 60 milligrams (mg) per day, once a day, on Day 3 through Day 23 of each 28-day treatment cycle.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was administered at a dose of 80 milligrams per square meter (mg/m^2) by intravenous (IV) infusion on Day 1, Day 8, and Day 15 of each 28-day cycle according to prescribing information.

Arm title	Cohort I: Placebo, Paclitaxel

Arm description:

Participants received a combination of cobimetinib placebo plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching to cobimetinib was administered orally, once a day, on Day 3 through Day 23 of each 28 day treatment cycle.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was administered at a dose of 80 milligrams per square meter (mg/m^2) by intravenous (IV) infusion on Day 1, Day 8, and Day 15 of each 28-day cycle according to prescribing information.

Arm title	Cohort II:Cobimetinib,Paclitaxel,Atezolizumab

Arm description:

Participants received cobimetinib plus paclitaxel plus atezolizumab in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab was administered to Cohorts II and III at a dose of 840 mg IV every 2 weeks on Days 1 and 15 of each 28-day treatment cycle.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was administered at a dose of 80 milligrams per square meter (mg/m^2) by intravenous (IV) infusion on Day 1, Day 8, and Day 15 of each 28-day cycle according to prescribing information.

Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	Cotellic
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib was administered orally at a dose of 60 milligrams (mg) per day, once a day, on Day 3 through Day 23 of each 28-day treatment cycle.

Arm title	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab

Arm description:

Participants received cobimetinib plus nab-paclitaxel plus atezolizumab until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

Arm type	Experimental
Investigational medicinal product name	Nab-Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nab-Paclitaxel was administered to Cohort III according to the local prescribing information at a starting dose of 100 mg/m^2 by IV infusion on Days 1, 8, and 15 of each 28 day cycle.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab was administered to Cohorts II and III at a dose of 840 mg IV every 2 weeks on Days 1 and 15 of each 28-day treatment cycle.

Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	Cotellic
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib was administered orally at a dose of 60 milligrams (mg) per day, once a day, on Day 3 through Day 23 of each 28-day treatment cycle.

Number of subjects in period 1	Cohort I: Safety Run-In	Cohort I: Cobimetinib, Paclitaxel	Cohort I: Placebo, Paclitaxel
Started	16	47	43
Completed	0	0	0
Not completed	16	47	43
Death	7	32	29
Progressive Disease	-	-	-
Withdrawal by Subject	5	2	4
Study Terminated by Sponsor	-	9	7
Lost to follow-up	1	3	3
Various Reasons	2	1	-
Protocol deviation	1	-	-

Number of subjects in period 1	Cohort II:Cobimetinib,Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab
Started	32	31
Completed	0	0
Not completed	32	31
Death	23	14
Progressive Disease	1	1
Withdrawal by Subject	1	3
Study Terminated by Sponsor	5	13
Lost to follow-up	1	-
Various Reasons	1	-
Protocol deviation	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort I: Safety Run-In
Reporting group description:	
Participants received cobimetinib plus paclitaxel until 12 participants completed one cycle of study treatment (28 days).	
Reporting group title	Cohort I: Cobimetinib, Paclitaxel
Reporting group description:	
Participants received a combination of cobimetinib plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.	
Reporting group title	Cohort I: Placebo, Paclitaxel
Reporting group description:	
Participants received a combination of cobimetinib placebo plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.	
Reporting group title	Cohort II:Cobimetinib,Paclitaxel,Atezolizumab
Reporting group description:	
Participants received cobimetinib plus paclitaxel plus atezolizumab in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.	
Reporting group title	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab
Reporting group description:	
Participants received cobimetinib plus nab-paclitaxel plus atezolizumab until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.	

Reporting group values	Cohort I: Safety Run-In	Cohort I: Cobimetinib, Paclitaxel	Cohort I: Placebo, Paclitaxel
Number of subjects	16	47	43
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	13	40	34
From 65-84 years	3	7	9
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	53.6	54.2	52.9
standard deviation	± 12.7	± 10.3	± 13.7
Gender Categorical Units: Subjects			
Female	16	47	43
Male	0	0	0

Race (NIH/OMB) Units: Subjects			
Asian	3	11	9
Black or African American	2	2	0
White	10	32	34
Other	1	0	0
Unknown	0	2	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	3	7
Not Hispanic or Latino	13	41	35
Not Stated	2	2	1
Unknown	0	1	0

Reporting group values	Cohort II:Cobimetinib,Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab	Total
Number of subjects	32	31	169
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	24	26	137
From 65-84 years	8	5	32
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	53.7	52.2	
standard deviation	± 13.1	± 11.8	-
Gender Categorical Units: Subjects			
Female	32	31	169
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
Asian	2	5	30
Black or African American	1	0	5
White	28	25	129
Other	1	1	3
Unknown	0	0	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	3	16
Not Hispanic or Latino	30	28	147
Not Stated	0	0	5
Unknown	0	0	1

End points

End points reporting groups

Reporting group title	Cohort I: Safety Run-In
Reporting group description:	
Participants received cobimetinib plus paclitaxel until 12 participants completed one cycle of study treatment (28 days).	
Reporting group title	Cohort I: Cobimetinib, Paclitaxel
Reporting group description:	
Participants received a combination of cobimetinib plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.	
Reporting group title	Cohort I: Placebo, Paclitaxel
Reporting group description:	
Participants received a combination of cobimetinib placebo plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.	
Reporting group title	Cohort II:Cobimetinib,Paclitaxel,Atezolizumab
Reporting group description:	
Participants received cobimetinib plus paclitaxel plus atezolizumab in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.	
Reporting group title	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab
Reporting group description:	
Participants received cobimetinib plus nab-paclitaxel plus atezolizumab until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.	

Primary: Cohort I: Progression-Free Survival, as Determined by Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point title	Cohort I: Progression-Free Survival, as Determined by Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)[1]
End point description:	
PFS was defined as the time from randomization to the first occurrence of disease progression or relapse, as determined by the investigator, using RECIST v1.1. As per RECIST v1.1, progressive disease (PD) is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimeters (mm). The appearance of one or more new lesions is also considered progression. Data were only collected from participants in the Cohort I Expansion Stage (Cohort I: Cobimetinib, Paclitaxel, Cohort I: Placebo, Paclitaxel) for this outcome measure. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received.	
End point type	Primary
End point timeframe:	
Randomization up to disease progression or relapse, whichever occurs first (up to approximately 2 years)	

Notes:

[1] - 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 primary objective was to estimate the clinical benefit of cobimetinib plus paclitaxel relative to placebo plus paclitaxel, as measured by investigator-assessed PFS, so only these two arms have data related to primary endpoint.

End point values	Cohort I: Cobimetinib, Paclitaxel	Cohort I: Placebo, Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	43		
Units: Weeks				
median (confidence interval 95%)	23.71 (18.14 to 32.14)	16.43 (8.14 to 31.14)		

Statistical analyses

Statistical analysis title	Cobimetinib vs. Placebo
Comparison groups	Cohort I: Placebo, Paclitaxel v Cohort I: Cobimetinib, Paclitaxel
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.247
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.24

Primary: Cohort II, III: Percentage of Participants With Confirmed Overall Response (OR) (Partial Response [PR] or Complete Response [CR]), as Determined by the Investigator Using RECIST v1.1

End point title	Cohort II, III: Percentage of Participants With Confirmed Overall Response (OR) (Partial Response [PR] or Complete Response [CR]), as Determined by the Investigator Using RECIST v1.1[2][3]

End point description:

OR was defined as the rate of a PR or CR occurring after randomization and confirmed >=28 days later as determined by the investigator using RECIST v1.1. As per RECIST v1.1, CR is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm. PR is defined as at least a 30% decrease in the sum of diameters of all target and new measurable lesions. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received.

End point type	Primary

End point timeframe:

Randomization up to disease progression or relapse, whichever occurs first (up to approximately 5.25 years)

Notes:

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

[3] - 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 analysis was only performed on Cohorts II and III and hence why not all arms are presented.

End point values	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: Percentage of participants				
number (not applicable)				
Responders	37.5	32.3		
Non-Responders	62.5	67.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II, III: Overall Survival (OS)

End point title	Cohort I, II, III: Overall Survival (OS)[4]

End point description:

OS was defined as the time from randomization to death from any cause. Data were only collected from participants in the Cohort I Expansion Stage (Cohort I: Cobimetinib, Paclitaxel, Cohort I: Placebo, Paclitaxel) along with the Cohort II and III for this outcome measure. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received. 9999999 = The upper limit of 95% CI was not evaluable due to insufficient events observed.

End point type	Secondary

End point timeframe:

Randomization up to death from any cause (up to approximately 6.5 years)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The analysis excludes the Safety Run-In cohort.

End point values	Cohort I: Cobimetinib, Paclitaxel	Cohort I: Placebo, Paclitaxel	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	43	32	31
Units: Months				
median (confidence interval 95%)	16.72 (13.50 to 20.24)	19.58 (14.75 to 29.37)	11.04 (9.53 to 22.51)	15.57 (14.26 to 9999999)

Statistical analyses

Statistical analysis title	Cohort I: Cobimetinib vs. Placebo
Comparison groups	Cohort I: Cobimetinib, Paclitaxel v Cohort I: Placebo, Paclitaxel

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5912
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	2.13

Secondary: Cohort I: Percentage of Participants With Confirmed OR (PR or CR), as Determined by the Investigator Using RECIST v1.1

End point title	Cohort I: Percentage of Participants With Confirmed OR (PR or CR), as Determined by the Investigator Using RECIST v1.1[5]

End point description:

OR was defined as the rate of a PR or CR occurring after randomization and confirmed >=28 days later as determined by the investigator using RECIST v1.1. As per RECIST v1.1, CR is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm. PR is defined as at least a 30% decrease in the sum of diameters of all target and new measurable lesions. Data were only collected from participants in the Cohort I Expansion Stage (Cohort I: Cobimetinib, Paclitaxel, Cohort I: Placebo, Paclitaxel) for this outcome measure. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received.

End point type	Secondary

End point timeframe:

Randomization up to disease progression or relapse, whichever occurs first (up to approximately 2 years)

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 analysis was only performed on Cohort I and hence why not all arms are presented.

End point values	Cohort I: Cobimetinib, Paclitaxel	Cohort I: Placebo, Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	43		
Units: Percentage of participants				
number (not applicable)				
Responders	38.3	20.9		
Non-Responders	61.7	79.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II, III: Duration of Response (DOR), as Determined by the

Investigator Using RECIST v1.1

End point title	Cohort I, II, III: Duration of Response (DOR), as Determined by the Investigator Using RECIST v1.1

End point description:

DOR was defined as the time from the first occurrence of a documented objective response to the time of relapse, as determined by the investigator using RECIST v1.1 or death from any cause during the study, whichever occurred first. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received. 9999999 = The upper limit of 95% CI was not evaluable due to insufficient events observed.

End point type	Secondary

End point timeframe:

Time from the first occurrence of documented objective response to time of relapse or death, whichever occurs first (up to approximately 6.5 years)

End point values	Cohort I: Safety Run-In	Cohort I: Cobimetinib, Paclitaxel	Cohort I: Placebo, Paclitaxel	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	47	43	32
Units: Months				
median (confidence interval 95%)	39.29 (23.14 to 56.29)	23.14 (16.14 to 26.57)	24.14 (17.14 to 9999999)	5.78 (4.44 to 16.33)

End point values	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Months				
median (confidence interval 95%)	11.42 (5.78 to 17.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II, III: Percentage of Participants With Unconfirmed Overall Response (OR_uc) (Unconfirmed PR or CR), as Determined by the Investigator Using RECIST v1.1

End point title	Cohort I, II, III: Percentage of Participants With Unconfirmed Overall Response (OR_uc) (Unconfirmed PR or CR), as Determined by the Investigator Using RECIST v1.1[6]

End point description:

ORR_uc (ORR confirmation not required) was defined as the rate of a PR or CR occurring after randomization as determined by the investigator using RECIST v1.1, confirmation not required. As per RECIST v1.1, CR is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm. PR is defined as at least a 30% decrease in the sum of diameters of all target and new measurable lesions. Data were only

collected from participants in the Cohort I Expansion Stage (Cohort I: Cobimetinib, Paclitaxel, Cohort I: Placebo, Paclitaxel) along with the Cohort II and III for this outcome measure. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received.

End point type	Secondary

End point timeframe:

Randomization up to disease progression or relapse, whichever occurs fist (up to approximately 6.5 years)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis excludes the Safety Run-In cohort.

End point values	Cohort I: Cobimetinib, Paclitaxel	Cohort I: Placebo, Paclitaxel	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	43	32	31
Units: Percentage of participants				
number (not applicable)				
Responders	42.6	25.6	46.9	45.2
Non-Responders	57.4	74.4	53.1	54.8

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort II, III: Progression-Free Survival, as Determined by Investigator Using RECIST v1.1

End point title	Cohort II, III: Progression-Free Survival, as Determined by Investigator Using RECIST v1.1[7]

End point description:

PFS was defined as the time from randomization to the first occurrence of disease progression or relapse, as determined by the investigator, using RECIST v1.1. As per RECIST v1.1, PD is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. 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 is also considered progression. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received.

End point type	Secondary

End point timeframe:

Randomization up to disease progression or relapse, whichever occurs first (up to approximately 6.5 years)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was only performed on Cohorts II and III and hence why not all arms are presented.

End point values	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: Months				
median (confidence interval 95%)	3.75 (3.02 to 7.29)	7.66 (3.65 to 11.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II, III: Percentage of Participants With Adverse Events (AEs)

End point title	Cohort I, II, III: Percentage of Participants With Adverse Events (AEs)

End point description:

The safety-evaluable population was defined as participants who received any amount of any study drug.

End point type	Secondary

End point timeframe:

Randomization up to end of study (up to approximately 6.5 years)

End point values	Cohort I: Safety Run-In	Cohort I: Cobimetinib, Paclitaxel	Cohort I: Placebo, Paclitaxel	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	47	43	32
Units: Percentage of participants				
number (not applicable)	93.8	97.9	100.0	100.0

End point values	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of participants				
number (not applicable)	100.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II, III: Maximum Plasma Concentration (Cmax) of Cobimetinib

End point title	Cohort I, II, III: Maximum Plasma Concentration (Cmax) of Cobimetinib[8]

End point description:

The pharmacokinetic (PK) population included all participants with evaluable PK data who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Safety Run-In: Predose (Hour [Hr] 0) on Cycle (Cy) 1 Day (D) 8; predose (Hr 0), 0.5, 1, 2, 4, 6 Hr postdose (2, 4 Hr postdose for Cohorts II, III) on Cy1 D15; Expansion: predose (Hr 0), 1-4 Hr postdose on Cy1 D15; predose (Hr 0) on Cy2 D15 (Cy=28 days)

Notes:

[8] - 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 analysis was only performed on the arms with Cobimetinib and hence why not all arms are presented.

End point values	Cohort I: Safety Run-In	Cohort I: Cobimetinib, Paclitaxel	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	17	15
Units: Nanograms per millilitre (ng/mL)				
geometric mean (geometric coefficient of variation)	285 (± 62.2)	266 (± 82.0)	213 (± 68.0)	407 (± 90.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II, III: Minimum Plasma Concentration (Cmin) of Cobimetinib

End point title	Cohort I, II, III: Minimum Plasma Concentration (Cmin) of Cobimetinib[9]

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy 1 D8; predose (Hr 0), 0.5, 1, 2, 4, 6 Hr postdose (2, 4 Hr postdose for Cohorts II, III) on Cy1 D15; Expansion: predose (Hr 0), 1-4 Hr postdose on Cy1 D15; predose (Hr 0) on Cy2 D15 (Cy=28 days)

Notes:

[9] - 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 analysis was only performed on the arms with Cobimetinib and hence why not all arms are presented.

End point values	Cohort I: Safety Run-In	Cohort I: Cobimetinib, Paclitaxel	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	38	14	13
Units: ng/mL				
geometric mean (geometric coefficient of variation)	65.6 (± 1279.5)	130 (± 190.7)	138 (± 79.0)	136 (± 67.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I: Area Under the Concentration-Time Curve From Time Zero to Dosing Interval (AUC0-tau; Total Exposure) of Cobimetinib

End point title	Cohort I: Area Under the Concentration-Time Curve From Time Zero to Dosing Interval (AUC0-tau; Total Exposure) of Cobimetinib[10]

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug. Data were only collected from participants in the Cohort I: Safety Run-In stage for this outcome measure.

End point type	Secondary

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy 1 D8; predose (Hr 0), 0.5, 1, 2, 4, 6 Hr postdose on Cy1 D15; Expansion: predose (Hr 0), 1-4 Hr postdose on Cy1 D15 (Cy=28 days)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was only performed on the arms with Cobimetinib and hence why not all arms are presented.

End point values	Cohort I: Safety Run-In			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Nanograms/milliliter/hour (hr*ng/mL)				
geometric mean (geometric coefficient of variation)	1620 (± 80.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II: Cmax of Paclitaxel

End point title	Cohort I, II: Cmax of Paclitaxel[11]

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug. Data were only collected from Cohort I: Safety Run-In and Cohort II participants for this

outcome measure.

End point type	Secondary

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy1 D8; predose (Hr 0), 0.5, 1, 2, 4, and 6 Hr postdose (2, 4 Hr postdose for Cohort II) (infusion duration: 1 Hr) on Cy1 D15 (Cy=28 days)

Notes:

[11] - 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 analysis was only performed on the arms with Paclitaxel and hence why not all arms are presented.

End point values	Cohort I: Safety Run-In	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	14		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	1770 (± 553.4)	283 (± 490.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II: Cmin of Paclitaxel

End point title	Cohort I, II: Cmin of Paclitaxel[12]

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug. Data were only collected from Cohort I: Safety Run-In and Cohort II participants for this outcome measure.

End point type	Secondary

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy1 D8; predose (Hr 0), 0.5, 1, 2, 4, and 6 Hr postdose (2, 4 Hr postdose for Cohort II) (infusion duration: 1 Hr) on Cy1 D15 (Cy=28 days)

Notes:

[12] - 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 analysis was only performed on the arms with Paclitaxel and hence why not all arms are presented.

End point values	Cohort I: Safety Run-In	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	15		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	1.40 (± 89.9)	1.26 (± 53.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I: AUC0-tau of Paclitaxel

End point title	Cohort I: AUC0-tau of Paclitaxel[13]

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug. Data were only collected from participants in the Cohort I: Safety Run-In stage for this outcome measure.

End point type	Secondary

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy1 D8; predose (Hr 0), 0.5, 1, 2, 4, and 6 Hr postdose (infusion duration: 1 Hr) on Cy1 D15 (Cy=28 days)

Notes:

[13] - 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 analysis was only performed on the arms with Paclitaxel and hence why not all arms are presented.

End point values	Cohort I: Safety Run-In			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	4220 (± 310.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort III: Cmax of Nab-Paclitaxel

End point title	Cohort III: Cmax of Nab-Paclitaxel[14]

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy1 D8; predose (Hr 0), 2, 4 Hr postdose (infusion duration: 30 minutes) on Cy1 D15 (Cy=28 days)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was only performed on the arms with Nab-Paclitaxel and hence why not all

arms are presented.

End point values	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	277 (± 658.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort III: Cmin of Nab-Paclitaxel

End point title	Cohort III: Cmin of Nab-Paclitaxel[15]

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy1 D8; predose (Hr 0), 2, 4 Hr postdose (infusion duration: 30 minutes) on Cy1 D15 (Cy=28 days)

Notes:

[15] - 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 analysis was only performed on the arms with Nab-Paclitaxel and hence why not all arms are presented.

End point values	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	2.05 (± 173.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort III: AUC0-tau of Nab-Paclitaxel

End point title	Cohort III: AUC0-tau of Nab-Paclitaxel[16]

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug. Due to the sparse nature of PK sampling, the estimation of this PK parameter requires the use of population PK analysis. This would have enabled the exposure-response analysis with this OM. Given the outcome of the study, the Sponsors did not proceed with popPK analysis, which was planned, only if data warranted. AUC0-tau was not estimated and analyzed using the sparse PK samples.

End point type	Secondary

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy1 D8; predose (Hr 0), 2, 4 Hr postdose (infusion duration: 30 minutes) on Cy1 D15 (Cy=28 days)

Notes:

[16] - 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 analysis was only performed on the arms with Nab-Paclitaxel and hence why not all arms are presented.

End point values	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[17]			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	()			

Notes:

[17] - Insufficient data was collected which precludes the calculation of this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort II, III: Cmax (in Serum) of Atezolizumab

End point title	Cohort II, III: Cmax (in Serum) of Atezolizumab[18]

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug

End point type	Secondary

End point timeframe:

Safety Run-In, Expansion:Predose (Hr0), 0.5Hr postdose (infusion duration:1Hr) on D1 of Cy1, 3; predose (Hr0) on D1 of Cy2, 4, 8, every 8 Cy up to end of treatment (EOT); 120 days after EOT (approximately 5.25 years) (Cy=28 days)

Notes:

[18] - 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 analysis was only performed on the arms with Atezolizumab and hence why not all arms are presented.

End point values	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: ng/mL				
geometric mean (geometric coefficient	346 (± 48.3)	374 (± 38.8)		

of variation)

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort II, III: Cmin (in Serum) of Atezolizumab

End point title	Cohort II, III: Cmin (in Serum) of Atezolizumab[19]

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug

End point type	Secondary

End point timeframe:

Safety Run-In, Expansion: Predose (Hr 0), 0.5 Hr postdose (infusion duration: 1 Hr) on D1 of Cy1, 3; predose (Hr 0) on D1 of Cy2, 4, 8, every 8 Cy up to EOT; 120 days after EOT (approximately 5.5 years) (Cy=28 days)

Notes:

[19] - 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 analysis was only performed on the arms with Atezolizumab and hence why not all arms are presented.

End point values	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	144 (± 34.6)	109 (± 89.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort II, III: AUC0-tau (in Serum) of Atezolizumab

End point title	Cohort II, III: AUC0-tau (in Serum) of Atezolizumab[20]

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug. Due to the sparse nature of PK sampling, the estimation of this PK parameter requires the use of population PK analysis. This would have enabled the exposure-response analysis with this OM. Given the outcome of the study, the Sponsors did not proceed with popPK analysis, which was planned, only if data warranted. AUC0-tau was not estimated and analyzed using the sparse PK samples.

End point type	Secondary

End point timeframe:

Safety Run-In, Expansion: Predose (Hr 0), 0.5 Hr postdose (infusion duration: 1 Hr) on D1 of Cy1, 3; predose (Hr 0) on D1 of Cy2, 4, 8, every 8 Cy up to EOT (approximately 5.5 years); 120 days after EOT

(approximately 5.5 years) (Cy=28 days)

Notes:

[20] - 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 analysis was only performed on the arms with Atezolizumab and hence why not all arms are presented.

End point values	Cohort II:Cobimetinib, Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[21]	0[22]		
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[21] - Insufficient data was collected which precludes the calculation of this outcome measure.

[22] - Insufficient data was collected which precludes the calculation of this outcome measure.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization up until 6.5 years

Adverse event reporting additional description:

The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Cohort I: Safety Run-In

Reporting group description:

Participants received cobimetinib plus paclitaxel until 12 participants completed one cycle of study treatment (28 days).

Reporting group title	Cohort I: Placebo, Paclitaxel

Reporting group description:

Participants received a combination of cobimetinib placebo plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

Reporting group title	Cohort I: Cobimetinib, Paclitaxel

Reporting group description:

Participants received a combination of cobimetinib plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

Reporting group title	Cohort II: Cobimetinib,Paclitaxel,Atezolizumab

Reporting group description:

Participants received cobimetinib plus paclitaxel plus atezolizumab in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

Reporting group title	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab

Reporting group description:

Participants received cobimetinib plus nab-paclitaxel plus atezolizumab until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

Serious adverse events	Cohort I: Safety Run-In	Cohort I: Placebo, Paclitaxel	Cohort I: Cobimetinib, Paclitaxel
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 16 (37.50%)	8 / 43 (18.60%)	17 / 47 (36.17%)
number of deaths (all causes)	7	29	32
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR HAEMORRHAGE			

subjects affected / exposed[1]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
EMBOLISM			
subjects affected / exposed[2]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
EMBOLISM VENOUS			
subjects affected / exposed[3]	0 / 16 (0.00%)	1 / 43 (2.33%)	0 / 47 (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
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed[4]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed[5]	2 / 16 (12.50%)	0 / 43 (0.00%)	6 / 47 (12.77%)
occurrences causally related to treatment / all	1 / 2	0 / 0	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUCOSAL INFLAMMATION			
subjects affected / exposed[6]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
ASTHENIA			
subjects affected / exposed[7]	1 / 16 (6.25%)	1 / 43 (2.33%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FATIGUE			
subjects affected / exposed[8]	0 / 16 (0.00%)	1 / 43 (2.33%)	0 / 47 (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

Respiratory, thoracic and mediastinal disorders			
EPISTAXIS			
subjects affected / exposed[9]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
DYSPNOEA			
subjects affected / exposed[10]	0 / 16 (0.00%)	1 / 43 (2.33%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG INFILTRATION			
subjects affected / exposed[11]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
PLEURITIC PAIN			
subjects affected / exposed[12]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONITIS			
subjects affected / exposed[13]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed[14]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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 FAILURE			
subjects affected / exposed[15]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed[16]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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

Cardiac disorders			
MITRAL VALVE INCOMPETENCE			
subjects affected / exposed[17]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (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
CARDIAC ARREST			
subjects affected / exposed[18]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
CARDIAC FAILURE			
subjects affected / exposed[19]	0 / 16 (0.00%)	1 / 43 (2.33%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
BRAIN OEDEMA			
subjects affected / exposed[20]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed[21]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENCEPHALOPATHY			
subjects affected / exposed[22]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
PRESYNCOPE			
subjects affected / exposed[23]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (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
PARTIAL SEIZURES			
subjects affected / exposed[24]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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

OPTIC NEURITIS			
subjects affected / exposed[25]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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 and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed[26]	0 / 16 (0.00%)	1 / 43 (2.33%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			
subjects affected / exposed[27]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
PAPILLOEDEMA			
subjects affected / exposed[28]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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			
DIARRHOEA			
subjects affected / exposed[29]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed[30]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
NAUSEA			
subjects affected / exposed[31]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
INTESTINAL OBSTRUCTION			

subjects affected / exposed[32]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
ABDOMINAL PAIN			
subjects affected / exposed[33]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
GASTRIC PERFORATION			
subjects affected / exposed[34]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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			
RASH			
subjects affected / exposed[35]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
RASH ERYTHEMATOUS			
subjects affected / exposed[36]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed[37]	0 / 16 (0.00%)	1 / 43 (2.33%)	0 / 47 (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			
PERIORBITAL CELLULITIS			
subjects affected / exposed[38]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
HERPES ZOSTER			
subjects affected / exposed[39]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

SEPSIS			
subjects affected / exposed[40]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed[41]	0 / 16 (0.00%)	0 / 43 (0.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed[42]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
CELLULITIS			
subjects affected / exposed[43]	0 / 16 (0.00%)	0 / 43 (0.00%)	4 / 47 (8.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
KIDNEY INFECTION			
subjects affected / exposed[44]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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[45]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
PYELONEPHRITIS ACUTE			
subjects affected / exposed[46]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STREPTOCOCCAL SEPSIS			
subjects affected / exposed[47]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			

subjects affected / exposed[48]	0 / 16 (0.00%)	1 / 43 (2.33%)	3 / 47 (6.38%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MASTITIS			
subjects affected / exposed[49]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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
ERYSIPELAS			
subjects affected / exposed[50]	1 / 16 (6.25%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPOKALAEMIA			
subjects affected / exposed[51]	0 / 16 (0.00%)	1 / 43 (2.33%)	0 / 47 (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
DECREASED APPETITE			
subjects affected / exposed[52]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (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

Serious adverse events	Cohort II: Cobimetinib,Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 32 (50.00%)	15 / 31 (48.39%)	
number of deaths (all causes)	23	14	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR HAEMORRHAGE			
subjects affected / exposed[1]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
EMBOLISM			

subjects affected / exposed[2]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLISM VENOUS			
subjects affected / exposed[3]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed[4]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed[5]	4 / 32 (12.50%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCOSAL INFLAMMATION			
subjects affected / exposed[6]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHENIA			
subjects affected / exposed[7]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed[8]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
EPISTAXIS			
subjects affected / exposed[9]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

DYSPNOEA			
subjects affected / exposed[10]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFILTRATION			
subjects affected / exposed[11]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PLEURITIC PAIN			
subjects affected / exposed[12]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed[13]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed[14]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed[15]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed[16]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
MITRAL VALVE INCOMPETENCE			
subjects affected / exposed[17]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

CARDIAC ARREST			
subjects affected / exposed[18]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed[19]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
BRAIN OEDEMA			
subjects affected / exposed[20]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed[21]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENCEPHALOPATHY			
subjects affected / exposed[22]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRESYNCOPE			
subjects affected / exposed[23]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARTIAL SEIZURES			
subjects affected / exposed[24]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OPTIC NEURITIS			
subjects affected / exposed[25]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

FEBRILE NEUTROPENIA			
subjects affected / exposed[26]	1 / 32 (3.13%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed[27]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
PAPILLOEDEMA			
subjects affected / exposed[28]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed[29]	2 / 32 (6.25%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed[30]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed[31]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed[32]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed[33]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

GASTRIC PERFORATION			
subjects affected / exposed[34]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed[35]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH ERYTHEMATOUS			
subjects affected / exposed[36]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed[37]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
PERIORBITAL CELLULITIS			
subjects affected / exposed[38]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed[39]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed[40]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			

subjects affected / exposed[41]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed[42]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed[43]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
KIDNEY INFECTION			
subjects affected / exposed[44]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed[45]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS ACUTE			
subjects affected / exposed[46]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STREPTOCOCCAL SEPSIS			
subjects affected / exposed[47]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed[48]	0 / 32 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MASTITIS			

subjects affected / exposed[49]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed[50]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
HYPOKALAEMIA			
subjects affected / exposed[51]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DECREASED APPETITE			
subjects affected / exposed[52]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in

Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.
[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.
[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.
[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.
[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.
[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.
[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.
[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.
[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.
[15] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.
[16] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
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Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort I: Safety Run-In	Cohort I: Placebo, Paclitaxel	Cohort I: Cobimetinib, Paclitaxel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)	43 / 43 (100.00%)	46 / 47 (97.87%)
Vascular disorders			
HOT FLUSH			
subjects affected / exposed[53]	0 / 16 (0.00%)	2 / 43 (4.65%)	1 / 47 (2.13%)
occurrences (all)	0	2	1
FLUSHING			
subjects affected / exposed[54]	1 / 16 (6.25%)	2 / 43 (4.65%)	1 / 47 (2.13%)
occurrences (all)	1	2	1
HYPOTENSION			
subjects affected / exposed[55]	1 / 16 (6.25%)	1 / 43 (2.33%)	0 / 47 (0.00%)
occurrences (all)	1	1	0
HYPERTENSION			
subjects affected / exposed[56]	0 / 16 (0.00%)	3 / 43 (6.98%)	4 / 47 (8.51%)
occurrences (all)	0	5	7
LYMPHOEDEMA			
subjects affected / exposed[57]	0 / 16 (0.00%)	1 / 43 (2.33%)	4 / 47 (8.51%)
occurrences (all)	0	3	4
General disorders and administration site conditions			
CHILLS			
subjects affected / exposed[58]	1 / 16 (6.25%)	0 / 43 (0.00%)	3 / 47 (6.38%)
occurrences (all)	1	0	3
PYREXIA			
subjects affected / exposed[59]	4 / 16 (25.00%)	8 / 43 (18.60%)	9 / 47 (19.15%)
occurrences (all)	7	13	15
GENERALISED OEDEMA			
subjects affected / exposed[60]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
OEDEMA			

subjects affected / exposed[61]	1 / 16 (6.25%)	2 / 43 (4.65%)	5 / 47 (10.64%)
occurrences (all)	1	2	7
GAIT DISTURBANCE			
subjects affected / exposed[62]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
MUCOSAL INFLAMMATION			
subjects affected / exposed[63]	1 / 16 (6.25%)	2 / 43 (4.65%)	4 / 47 (8.51%)
occurrences (all)	3	3	9
FATIGUE			
subjects affected / exposed[64]	3 / 16 (18.75%)	15 / 43 (34.88%)	13 / 47 (27.66%)
occurrences (all)	3	19	15
PERIPHERAL SWELLING			
subjects affected / exposed[65]	1 / 16 (6.25%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
OEDEMA PERIPHERAL			
subjects affected / exposed[66]	4 / 16 (25.00%)	9 / 43 (20.93%)	9 / 47 (19.15%)
occurrences (all)	4	9	12
CHEST PAIN			
subjects affected / exposed[67]	0 / 16 (0.00%)	7 / 43 (16.28%)	5 / 47 (10.64%)
occurrences (all)	0	9	5
ASTHENIA			
subjects affected / exposed[68]	3 / 16 (18.75%)	11 / 43 (25.58%)	13 / 47 (27.66%)
occurrences (all)	3	18	15
INFLUENZA LIKE ILLNESS			
subjects affected / exposed[69]	0 / 16 (0.00%)	0 / 43 (0.00%)	3 / 47 (6.38%)
occurrences (all)	0	0	3
PAIN			
subjects affected / exposed[70]	1 / 16 (6.25%)	3 / 43 (6.98%)	3 / 47 (6.38%)
occurrences (all)	1	3	3
Reproductive system and breast disorders			
CYSTOCELE			
subjects affected / exposed[71]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
BREAST PAIN			

subjects affected / exposed[72]	0 / 16 (0.00%)	3 / 43 (6.98%)	1 / 47 (2.13%)
occurrences (all)	0	5	1
Respiratory, thoracic and mediastinal disorders			
PRODUCTIVE COUGH			
subjects affected / exposed[73]	1 / 16 (6.25%)	3 / 43 (6.98%)	1 / 47 (2.13%)
occurrences (all)	1	3	1
NASAL DRYNESS			
subjects affected / exposed[74]	2 / 16 (12.50%)	0 / 43 (0.00%)	2 / 47 (4.26%)
occurrences (all)	2	0	2
PLEURAL EFFUSION			
subjects affected / exposed[75]	0 / 16 (0.00%)	1 / 43 (2.33%)	3 / 47 (6.38%)
occurrences (all)	0	1	3
DYSPHONIA			
subjects affected / exposed[76]	2 / 16 (12.50%)	3 / 43 (6.98%)	2 / 47 (4.26%)
occurrences (all)	2	3	3
PULMONARY EMBOLISM			
subjects affected / exposed[77]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
PNEUMONITIS			
subjects affected / exposed[78]	0 / 16 (0.00%)	1 / 43 (2.33%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
OROPHARYNGEAL PAIN			
subjects affected / exposed[79]	0 / 16 (0.00%)	1 / 43 (2.33%)	4 / 47 (8.51%)
occurrences (all)	0	1	4
EPISTAXIS			
subjects affected / exposed[80]	2 / 16 (12.50%)	4 / 43 (9.30%)	4 / 47 (8.51%)
occurrences (all)	2	5	5
DYSPNOEA			
subjects affected / exposed[81]	4 / 16 (25.00%)	3 / 43 (6.98%)	7 / 47 (14.89%)
occurrences (all)	5	6	12
COUGH			
subjects affected / exposed[82]	2 / 16 (12.50%)	12 / 43 (27.91%)	7 / 47 (14.89%)
occurrences (all)	2	14	8
Psychiatric disorders			

INSOMNIA			
subjects affected / exposed[83]	2 / 16 (12.50%)	7 / 43 (16.28%)	3 / 47 (6.38%)
occurrences (all)	2	8	3
ANXIETY			
subjects affected / exposed[84]	0 / 16 (0.00%)	1 / 43 (2.33%)	2 / 47 (4.26%)
occurrences (all)	0	1	3
Investigations			
TRANSFERRIN SATURATION DECREASED			
subjects affected / exposed[85]	1 / 16 (6.25%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
BLOOD POTASSIUM DECREASED			
subjects affected / exposed[86]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed[87]	0 / 16 (0.00%)	1 / 43 (2.33%)	2 / 47 (4.26%)
occurrences (all)	0	1	2
WEIGHT DECREASED			
subjects affected / exposed[88]	0 / 16 (0.00%)	3 / 43 (6.98%)	0 / 47 (0.00%)
occurrences (all)	0	4	0
EJECTION FRACTION DECREASED			
subjects affected / exposed[89]	0 / 16 (0.00%)	0 / 43 (0.00%)	3 / 47 (6.38%)
occurrences (all)	0	0	3
CARBOHYDRATE ANTIGEN 15-3 INCREASED			
subjects affected / exposed[90]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed[91]	6 / 16 (37.50%)	0 / 43 (0.00%)	10 / 47 (21.28%)
occurrences (all)	6	0	10
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed[92]	3 / 16 (18.75%)	2 / 43 (4.65%)	3 / 47 (6.38%)
occurrences (all)	5	2	5
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed[93]	2 / 16 (12.50%)	3 / 43 (6.98%)	3 / 47 (6.38%)
occurrences (all)	4	5	4

GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed[94]	1 / 16 (6.25%)	2 / 43 (4.65%)	1 / 47 (2.13%)
occurrences (all)	1	5	1
PLATELET COUNT DECREASED			
subjects affected / exposed[95]	1 / 16 (6.25%)	1 / 43 (2.33%)	0 / 47 (0.00%)
occurrences (all)	1	2	0
HAEMOGLOBIN DECREASED			
subjects affected / exposed[96]	1 / 16 (6.25%)	2 / 43 (4.65%)	1 / 47 (2.13%)
occurrences (all)	1	2	1
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed[97]	0 / 16 (0.00%)	1 / 43 (2.33%)	3 / 47 (6.38%)
occurrences (all)	0	2	3
FIBRIN D DIMER INCREASED			
subjects affected / exposed[98]	2 / 16 (12.50%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
SERUM FERRITIN INCREASED			
subjects affected / exposed[99]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
WHITE BLOOD CELL COUNT INCREASED			
subjects affected / exposed[100]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed[101]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
MYOGLOBIN BLOOD INCREASED			
subjects affected / exposed[102]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
NEUTROPHIL COUNT INCREASED			
subjects affected / exposed[103]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED			
subjects affected / exposed[104]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
C-REACTIVE PROTEIN INCREASED			

subjects affected / exposed[105]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
BLOOD PRESSURE INCREASED			
subjects affected / exposed[106]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
CHEST INJURY			
subjects affected / exposed[107]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
INFUSION RELATED REACTION			
subjects affected / exposed[108]	2 / 16 (12.50%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	3	0	0
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed[109]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
PALPITATIONS			
subjects affected / exposed[110]	1 / 16 (6.25%)	1 / 43 (2.33%)	2 / 47 (4.26%)
occurrences (all)	1	1	2
Nervous system disorders			
DYSGEUSIA			
subjects affected / exposed[111]	1 / 16 (6.25%)	4 / 43 (9.30%)	7 / 47 (14.89%)
occurrences (all)	1	4	7
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed[112]	2 / 16 (12.50%)	9 / 43 (20.93%)	8 / 47 (17.02%)
occurrences (all)	2	12	12
PARAESTHESIA			
subjects affected / exposed[113]	0 / 16 (0.00%)	5 / 43 (11.63%)	4 / 47 (8.51%)
occurrences (all)	0	9	5
DYSMETRIA			
subjects affected / exposed[114]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
NEUROTOXICITY			
subjects affected / exposed[115]	0 / 16 (0.00%)	3 / 43 (6.98%)	0 / 47 (0.00%)
occurrences (all)	0	4	0
HYPOGEUSIA			

subjects affected / exposed[116]	2 / 16 (12.50%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
HYPOAESTHESIA			
subjects affected / exposed[117]	1 / 16 (6.25%)	2 / 43 (4.65%)	3 / 47 (6.38%)
occurrences (all)	1	2	3
DYSTONIC TREMOR			
subjects affected / exposed[118]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
DIZZINESS			
subjects affected / exposed[119]	3 / 16 (18.75%)	8 / 43 (18.60%)	7 / 47 (14.89%)
occurrences (all)	3	9	9
HEADACHE			
subjects affected / exposed[120]	3 / 16 (18.75%)	9 / 43 (20.93%)	7 / 47 (14.89%)
occurrences (all)	3	14	14
NEUROPATHY PERIPHERAL			
subjects affected / exposed[121]	1 / 16 (6.25%)	7 / 43 (16.28%)	4 / 47 (8.51%)
occurrences (all)	1	10	4
Blood and lymphatic system disorders			
NEUTROPENIA			
subjects affected / exposed[122]	2 / 16 (12.50%)	13 / 43 (30.23%)	8 / 47 (17.02%)
occurrences (all)	16	43	21
LEUKOPENIA			
subjects affected / exposed[123]	1 / 16 (6.25%)	1 / 43 (2.33%)	1 / 47 (2.13%)
occurrences (all)	6	2	1
EOSINOPHILIA			
subjects affected / exposed[124]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
ANAEMIA			
subjects affected / exposed[125]	3 / 16 (18.75%)	6 / 43 (13.95%)	12 / 47 (25.53%)
occurrences (all)	3	9	16
Ear and labyrinth disorders			
TINNITUS			
subjects affected / exposed[126]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

VITREOUS FLOATERS			
subjects affected / exposed[127]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
VISION BLURRED			
subjects affected / exposed[128]	0 / 16 (0.00%)	1 / 43 (2.33%)	10 / 47 (21.28%)
occurrences (all)	0	1	11
CHORIORETINOPATHY			
subjects affected / exposed[129]	1 / 16 (6.25%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
CATARACT CORTICAL			
subjects affected / exposed[130]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
EPISCLERITIS			
subjects affected / exposed[131]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
MACULAR OEDEMA			
subjects affected / exposed[132]	0 / 16 (0.00%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
MACULAR FIBROSIS			
subjects affected / exposed[133]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
EYE PAIN			
subjects affected / exposed[134]	1 / 16 (6.25%)	0 / 43 (0.00%)	2 / 47 (4.26%)
occurrences (all)	1	0	2
EYELID OEDEMA			
subjects affected / exposed[135]	1 / 16 (6.25%)	1 / 43 (2.33%)	2 / 47 (4.26%)
occurrences (all)	1	1	2
CATARACT			
subjects affected / exposed[136]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
RETINAL DETACHMENT			
subjects affected / exposed[137]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
RETINAL DRUSEN			
subjects affected / exposed[138]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0

CONJUNCTIVAL HAEMORRHAGE			
subjects affected / exposed[139]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
DRY EYE			
subjects affected / exposed[140]	0 / 16 (0.00%)	3 / 43 (6.98%)	4 / 47 (8.51%)
occurrences (all)	0	3	4
Gastrointestinal disorders			
DRY MOUTH			
subjects affected / exposed[141]	2 / 16 (12.50%)	1 / 43 (2.33%)	6 / 47 (12.77%)
occurrences (all)	2	1	6
APHTHOUS ULCER			
subjects affected / exposed[142]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
VOMITING			
subjects affected / exposed[143]	5 / 16 (31.25%)	7 / 43 (16.28%)	8 / 47 (17.02%)
occurrences (all)	6	8	13
CONSTIPATION			
subjects affected / exposed[144]	4 / 16 (25.00%)	9 / 43 (20.93%)	8 / 47 (17.02%)
occurrences (all)	4	11	11
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed[145]	2 / 16 (12.50%)	1 / 43 (2.33%)	2 / 47 (4.26%)
occurrences (all)	6	1	2
DYSPHAGIA			
subjects affected / exposed[146]	0 / 16 (0.00%)	2 / 43 (4.65%)	2 / 47 (4.26%)
occurrences (all)	0	2	2
MOUTH ULCERATION			
subjects affected / exposed[147]	0 / 16 (0.00%)	0 / 43 (0.00%)	2 / 47 (4.26%)
occurrences (all)	0	0	3
HAEMORRHOIDS			
subjects affected / exposed[148]	1 / 16 (6.25%)	2 / 43 (4.65%)	1 / 47 (2.13%)
occurrences (all)	1	2	2
ABDOMINAL PAIN UPPER			
subjects affected / exposed[149]	1 / 16 (6.25%)	4 / 43 (9.30%)	6 / 47 (12.77%)
occurrences (all)	1	5	6
STOMATITIS			

subjects affected / exposed[150]	5 / 16 (31.25%)	5 / 43 (11.63%)	13 / 47 (27.66%)
occurrences (all)	8	5	18
DIARRHOEA			
subjects affected / exposed[151]	10 / 16 (62.50%)	13 / 43 (30.23%)	36 / 47 (76.60%)
occurrences (all)	29	19	66
ABDOMINAL PAIN			
subjects affected / exposed[152]	3 / 16 (18.75%)	3 / 43 (6.98%)	5 / 47 (10.64%)
occurrences (all)	3	3	6
NAUSEA			
subjects affected / exposed[153]	7 / 16 (43.75%)	18 / 43 (41.86%)	20 / 47 (42.55%)
occurrences (all)	7	25	24
ABDOMINAL DISTENSION			
subjects affected / exposed[154]	1 / 16 (6.25%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
DYSPEPSIA			
subjects affected / exposed[155]	0 / 16 (0.00%)	3 / 43 (6.98%)	6 / 47 (12.77%)
occurrences (all)	0	3	9
Skin and subcutaneous tissue disorders			
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed[156]	1 / 16 (6.25%)	1 / 43 (2.33%)	0 / 47 (0.00%)
occurrences (all)	4	1	0
RASH			
subjects affected / exposed[157]	8 / 16 (50.00%)	5 / 43 (11.63%)	22 / 47 (46.81%)
occurrences (all)	18	6	34
SKIN LESION			
subjects affected / exposed[158]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
PRURITUS			
subjects affected / exposed[159]	2 / 16 (12.50%)	2 / 43 (4.65%)	12 / 47 (25.53%)
occurrences (all)	2	2	17
DERMATITIS ACNEIFORM			
subjects affected / exposed[160]	3 / 16 (18.75%)	3 / 43 (6.98%)	9 / 47 (19.15%)
occurrences (all)	3	4	12
INGROWING NAIL			

subjects affected / exposed[161]	1 / 16 (6.25%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
DRY SKIN			
subjects affected / exposed[162]	1 / 16 (6.25%)	0 / 43 (0.00%)	6 / 47 (12.77%)
occurrences (all)	1	0	7
ERYTHEMA			
subjects affected / exposed[163]	1 / 16 (6.25%)	1 / 43 (2.33%)	2 / 47 (4.26%)
occurrences (all)	1	1	3
RASH MACULO-PAPULAR			
subjects affected / exposed[164]	0 / 16 (0.00%)	1 / 43 (2.33%)	1 / 47 (2.13%)
occurrences (all)	0	1	1
NAIL DISCOLOURATION			
subjects affected / exposed[165]	1 / 16 (6.25%)	1 / 43 (2.33%)	3 / 47 (6.38%)
occurrences (all)	1	1	3
SKIN FISSURES			
subjects affected / exposed[166]	0 / 16 (0.00%)	0 / 43 (0.00%)	3 / 47 (6.38%)
occurrences (all)	0	0	4
RASH PAPULAR			
subjects affected / exposed[167]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
NAIL RIDGING			
subjects affected / exposed[168]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
ONYCHOMADESIS			
subjects affected / exposed[169]	1 / 16 (6.25%)	0 / 43 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
ERYTHEMA NODOSUM			
subjects affected / exposed[170]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
ALOPECIA			
subjects affected / exposed[171]	5 / 16 (31.25%)	19 / 43 (44.19%)	21 / 47 (44.68%)
occurrences (all)	5	20	22
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed[172]	0 / 16 (0.00%)	0 / 43 (0.00%)	3 / 47 (6.38%)
occurrences (all)	0	0	3

ACUTE KIDNEY INJURY			
subjects affected / exposed[173]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
DYSURIA			
subjects affected / exposed[174]	1 / 16 (6.25%)	1 / 43 (2.33%)	4 / 47 (8.51%)
occurrences (all)	1	1	5
Endocrine disorders			
HYPOTHYROIDISM			
subjects affected / exposed[175]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
MUSCLE SPASMS			
subjects affected / exposed[176]	1 / 16 (6.25%)	2 / 43 (4.65%)	1 / 47 (2.13%)
occurrences (all)	1	2	1
MUSCULAR WEAKNESS			
subjects affected / exposed[177]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
ARTHRALGIA			
subjects affected / exposed[178]	2 / 16 (12.50%)	7 / 43 (16.28%)	2 / 47 (4.26%)
occurrences (all)	2	9	4
BONE PAIN			
subjects affected / exposed[179]	1 / 16 (6.25%)	4 / 43 (9.30%)	1 / 47 (2.13%)
occurrences (all)	1	5	1
NECK PAIN			
subjects affected / exposed[180]	0 / 16 (0.00%)	1 / 43 (2.33%)	2 / 47 (4.26%)
occurrences (all)	0	1	2
BACK PAIN			
subjects affected / exposed[181]	2 / 16 (12.50%)	2 / 43 (4.65%)	6 / 47 (12.77%)
occurrences (all)	2	2	6
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed[182]	0 / 16 (0.00%)	2 / 43 (4.65%)	2 / 47 (4.26%)
occurrences (all)	0	2	2
MYALGIA			
subjects affected / exposed[183]	2 / 16 (12.50%)	6 / 43 (13.95%)	6 / 47 (12.77%)
occurrences (all)	2	8	8
JOINT SWELLING			

subjects affected / exposed[184]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
PAIN IN EXTREMITY			
subjects affected / exposed[185]	1 / 16 (6.25%)	5 / 43 (11.63%)	2 / 47 (4.26%)
occurrences (all)	1	5	2
Infections and infestations			
SINUSITIS			
subjects affected / exposed[186]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
RASH PUSTULAR			
subjects affected / exposed[187]	0 / 16 (0.00%)	1 / 43 (2.33%)	1 / 47 (2.13%)
occurrences (all)	0	1	1
FURUNCLE			
subjects affected / exposed[188]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
INFLUENZA			
subjects affected / exposed[189]	1 / 16 (6.25%)	1 / 43 (2.33%)	0 / 47 (0.00%)
occurrences (all)	1	1	0
NASOPHARYNGITIS			
subjects affected / exposed[190]	1 / 16 (6.25%)	1 / 43 (2.33%)	2 / 47 (4.26%)
occurrences (all)	1	1	4
PARONYCHIA			
subjects affected / exposed[191]	1 / 16 (6.25%)	2 / 43 (4.65%)	4 / 47 (8.51%)
occurrences (all)	1	4	5
VAGINAL INFECTION			
subjects affected / exposed[192]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
LOCALISED INFECTION			
subjects affected / exposed[193]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed[194]	2 / 16 (12.50%)	4 / 43 (9.30%)	3 / 47 (6.38%)
occurrences (all)	4	6	3
PNEUMONIA			

subjects affected / exposed[195]	0 / 16 (0.00%)	1 / 43 (2.33%)	3 / 47 (6.38%)
occurrences (all)	0	1	3
LYMPHANGITIS			
subjects affected / exposed[196]	0 / 16 (0.00%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
CYSTITIS			
subjects affected / exposed[197]	0 / 16 (0.00%)	1 / 43 (2.33%)	3 / 47 (6.38%)
occurrences (all)	0	1	4
ORAL HERPES			
subjects affected / exposed[198]	0 / 16 (0.00%)	1 / 43 (2.33%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
PHARYNGITIS			
subjects affected / exposed[199]	0 / 16 (0.00%)	0 / 43 (0.00%)	3 / 47 (6.38%)
occurrences (all)	0	0	3
CELLULITIS			
subjects affected / exposed[200]	0 / 16 (0.00%)	1 / 43 (2.33%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
NAIL INFECTION			
subjects affected / exposed[201]	0 / 16 (0.00%)	0 / 43 (0.00%)	2 / 47 (4.26%)
occurrences (all)	0	0	2
LARYNGITIS			
subjects affected / exposed[202]	1 / 16 (6.25%)	0 / 43 (0.00%)	2 / 47 (4.26%)
occurrences (all)	1	0	2
IMPETIGO			
subjects affected / exposed[203]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
URINARY TRACT INFECTION			
subjects affected / exposed[204]	2 / 16 (12.50%)	1 / 43 (2.33%)	4 / 47 (8.51%)
occurrences (all)	3	4	6
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed[205]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
HYPOMAGNESAEMIA			
subjects affected / exposed[206]	1 / 16 (6.25%)	0 / 43 (0.00%)	2 / 47 (4.26%)
occurrences (all)	1	0	3

DECREASED APPETITE			
subjects affected / exposed[207]	3 / 16 (18.75%)	10 / 43 (23.26%)	9 / 47 (19.15%)
occurrences (all)	3	14	11
HYPOPHOSPHATAEMIA			
subjects affected / exposed[208]	0 / 16 (0.00%)	1 / 43 (2.33%)	2 / 47 (4.26%)
occurrences (all)	0	1	3
HYPOKALAEMIA			
subjects affected / exposed[209]	0 / 16 (0.00%)	1 / 43 (2.33%)	5 / 47 (10.64%)
occurrences (all)	0	1	8
DIABETES MELLITUS			
subjects affected / exposed[210]	1 / 16 (6.25%)	0 / 43 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Cohort II: Cobimetinib,Paclitaxel,Atezolizumab	Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 32 (100.00%)	29 / 31 (93.55%)	
Vascular disorders			
HOT FLUSH			
subjects affected / exposed[53]	3 / 32 (9.38%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
FLUSHING			
subjects affected / exposed[54]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
HYPOTENSION			
subjects affected / exposed[55]	2 / 32 (6.25%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
HYPERTENSION			
subjects affected / exposed[56]	1 / 32 (3.13%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
LYMPHOEDEMA			
subjects affected / exposed[57]	3 / 32 (9.38%)	2 / 30 (6.67%)	
occurrences (all)	5	2	
General disorders and administration site conditions			
CHILLS			

subjects affected / exposed[58]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
PYREXIA			
subjects affected / exposed[59]	1 / 32 (3.13%)	9 / 30 (30.00%)	
occurrences (all)	1	12	
GENERALISED OEDEMA			
subjects affected / exposed[60]	0 / 32 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
OEDEMA			
subjects affected / exposed[61]	0 / 32 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	4	
GAIT DISTURBANCE			
subjects affected / exposed[62]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
MUCOSAL INFLAMMATION			
subjects affected / exposed[63]	5 / 32 (15.63%)	5 / 30 (16.67%)	
occurrences (all)	6	9	
FATIGUE			
subjects affected / exposed[64]	11 / 32 (34.38%)	10 / 30 (33.33%)	
occurrences (all)	16	10	
PERIPHERAL SWELLING			
subjects affected / exposed[65]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
OEDEMA PERIPHERAL			
subjects affected / exposed[66]	7 / 32 (21.88%)	5 / 30 (16.67%)	
occurrences (all)	12	6	
CHEST PAIN			
subjects affected / exposed[67]	2 / 32 (6.25%)	1 / 30 (3.33%)	
occurrences (all)	4	1	
ASTHENIA			
subjects affected / exposed[68]	6 / 32 (18.75%)	6 / 30 (20.00%)	
occurrences (all)	11	8	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed[69]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
PAIN			

subjects affected / exposed[70]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
CYSTOCELE			
subjects affected / exposed[71]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
BREAST PAIN			
subjects affected / exposed[72]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
PRODUCTIVE COUGH			
subjects affected / exposed[73]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
NASAL DRYNESS			
subjects affected / exposed[74]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
PLEURAL EFFUSION			
subjects affected / exposed[75]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
DYSPHONIA			
subjects affected / exposed[76]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
PULMONARY EMBOLISM			
subjects affected / exposed[77]	1 / 32 (3.13%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
PNEUMONITIS			
subjects affected / exposed[78]	2 / 32 (6.25%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
OROPHARYNGEAL PAIN			
subjects affected / exposed[79]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
EPISTAXIS			
subjects affected / exposed[80]	7 / 32 (21.88%)	7 / 30 (23.33%)	
occurrences (all)	8	8	
DYSPNOEA			

subjects affected / exposed[81]	3 / 32 (9.38%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
COUGH			
subjects affected / exposed[82]	6 / 32 (18.75%)	5 / 30 (16.67%)	
occurrences (all)	7	6	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed[83]	3 / 32 (9.38%)	4 / 30 (13.33%)	
occurrences (all)	3	5	
ANXIETY			
subjects affected / exposed[84]	1 / 32 (3.13%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Investigations			
TRANSFERRIN SATURATION DECREASED			
subjects affected / exposed[85]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
BLOOD POTASSIUM DECREASED			
subjects affected / exposed[86]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed[87]	4 / 32 (12.50%)	4 / 30 (13.33%)	
occurrences (all)	9	7	
WEIGHT DECREASED			
subjects affected / exposed[88]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
EJECTION FRACTION DECREASED			
subjects affected / exposed[89]	1 / 32 (3.13%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
CARBOHYDRATE ANTIGEN 15-3 INCREASED			
subjects affected / exposed[90]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed[91]	5 / 32 (15.63%)	7 / 30 (23.33%)	
occurrences (all)	11	13	
ASPARTATE AMINOTRANSFERASE			

INCREASED			
subjects affected / exposed[92]	4 / 32 (12.50%)	5 / 30 (16.67%)	
occurrences (all)	6	7	
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed[93]	4 / 32 (12.50%)	6 / 30 (20.00%)	
occurrences (all)	7	7	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed[94]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
PLATELET COUNT DECREASED			
subjects affected / exposed[95]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
HAEMOGLOBIN DECREASED			
subjects affected / exposed[96]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed[97]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
FIBRIN D DIMER INCREASED			
subjects affected / exposed[98]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
SERUM FERRITIN INCREASED			
subjects affected / exposed[99]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
WHITE BLOOD CELL COUNT INCREASED			
subjects affected / exposed[100]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed[101]	3 / 32 (9.38%)	0 / 30 (0.00%)	
occurrences (all)	9	0	
MYOGLOBIN BLOOD INCREASED			
subjects affected / exposed[102]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
NEUTROPHIL COUNT INCREASED			

subjects affected / exposed[103]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
BLOOD THYROID STIMULATING HORMONE INCREASED			
subjects affected / exposed[104]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed[105]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
BLOOD PRESSURE INCREASED			
subjects affected / exposed[106]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
CHEST INJURY			
subjects affected / exposed[107]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
INFUSION RELATED REACTION			
subjects affected / exposed[108]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed[109]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
PALPITATIONS			
subjects affected / exposed[110]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
DYSGEUSIA			
subjects affected / exposed[111]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	1	3	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed[112]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
PARAESTHESIA			
subjects affected / exposed[113]	4 / 32 (12.50%)	0 / 30 (0.00%)	
occurrences (all)	5	0	
DYSMETRIA			

subjects affected / exposed[114]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
NEUROTOXICITY			
subjects affected / exposed[115]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
HYPOGEUSIA			
subjects affected / exposed[116]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
HYPOAESTHESIA			
subjects affected / exposed[117]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
DYSTONIC TREMOR			
subjects affected / exposed[118]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
DIZZINESS			
subjects affected / exposed[119]	4 / 32 (12.50%)	3 / 30 (10.00%)	
occurrences (all)	4	3	
HEADACHE			
subjects affected / exposed[120]	5 / 32 (15.63%)	4 / 30 (13.33%)	
occurrences (all)	7	6	
NEUROPATHY PERIPHERAL			
subjects affected / exposed[121]	8 / 32 (25.00%)	7 / 30 (23.33%)	
occurrences (all)	9	11	
Blood and lymphatic system disorders			
NEUTROPENIA			
subjects affected / exposed[122]	6 / 32 (18.75%)	8 / 30 (26.67%)	
occurrences (all)	6	18	
LEUKOPENIA			
subjects affected / exposed[123]	0 / 32 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	9	
EOSINOPHILIA			
subjects affected / exposed[124]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
ANAEMIA			
subjects affected / exposed[125]	14 / 32 (43.75%)	10 / 30 (33.33%)	
occurrences (all)	19	24	

Ear and labyrinth disorders			
TINNITUS			
subjects affected / exposed[126]	3 / 32 (9.38%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
VITREOUS FLOATERS			
subjects affected / exposed[127]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
VISION BLURRED			
subjects affected / exposed[128]	4 / 32 (12.50%)	4 / 30 (13.33%)	
occurrences (all)	4	5	
CHORIORETINOPATHY			
subjects affected / exposed[129]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
CATARACT CORTICAL			
subjects affected / exposed[130]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
EPISCLERITIS			
subjects affected / exposed[131]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
MACULAR OEDEMA			
subjects affected / exposed[132]	0 / 32 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	3	
MACULAR FIBROSIS			
subjects affected / exposed[133]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
EYE PAIN			
subjects affected / exposed[134]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
EYELID OEDEMA			
subjects affected / exposed[135]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
CATARACT			
subjects affected / exposed[136]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
RETINAL DETACHMENT			

subjects affected / exposed[137]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
RETINAL DRUSEN			
subjects affected / exposed[138]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
CONJUNCTIVAL HAEMORRHAGE			
subjects affected / exposed[139]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
DRY EYE			
subjects affected / exposed[140]	0 / 32 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
DRY MOUTH			
subjects affected / exposed[141]	0 / 32 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
APHTHOUS ULCER			
subjects affected / exposed[142]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
VOMITING			
subjects affected / exposed[143]	9 / 32 (28.13%)	12 / 30 (40.00%)	
occurrences (all)	16	16	
CONSTIPATION			
subjects affected / exposed[144]	6 / 32 (18.75%)	8 / 30 (26.67%)	
occurrences (all)	7	13	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed[145]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
DYSPHAGIA			
subjects affected / exposed[146]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
MOUTH ULCERATION			
subjects affected / exposed[147]	2 / 32 (6.25%)	2 / 30 (6.67%)	
occurrences (all)	2	3	
HAEMORRHOIDS			

subjects affected / exposed[148]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed[149]	2 / 32 (6.25%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
STOMATITIS			
subjects affected / exposed[150]	5 / 32 (15.63%)	5 / 30 (16.67%)	
occurrences (all)	5	11	
DIARRHOEA			
subjects affected / exposed[151]	21 / 32 (65.63%)	27 / 30 (90.00%)	
occurrences (all)	48	55	
ABDOMINAL PAIN			
subjects affected / exposed[152]	6 / 32 (18.75%)	5 / 30 (16.67%)	
occurrences (all)	8	6	
NAUSEA			
subjects affected / exposed[153]	13 / 32 (40.63%)	15 / 30 (50.00%)	
occurrences (all)	18	20	
ABDOMINAL DISTENSION			
subjects affected / exposed[154]	0 / 32 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
DYSPEPSIA			
subjects affected / exposed[155]	1 / 32 (3.13%)	5 / 30 (16.67%)	
occurrences (all)	1	7	
Skin and subcutaneous tissue disorders			
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed[156]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
RASH			
subjects affected / exposed[157]	12 / 32 (37.50%)	17 / 30 (56.67%)	
occurrences (all)	22	22	
SKIN LESION			
subjects affected / exposed[158]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
PRURITUS			

subjects affected / exposed[159]	4 / 32 (12.50%)	4 / 30 (13.33%)	
occurrences (all)	5	9	
DERMATITIS ACNEIFORM			
subjects affected / exposed[160]	8 / 32 (25.00%)	6 / 30 (20.00%)	
occurrences (all)	14	6	
INGROWING NAIL			
subjects affected / exposed[161]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
DRY SKIN			
subjects affected / exposed[162]	4 / 32 (12.50%)	5 / 30 (16.67%)	
occurrences (all)	5	7	
ERYTHEMA			
subjects affected / exposed[163]	1 / 32 (3.13%)	3 / 30 (10.00%)	
occurrences (all)	1	4	
RASH MACULO-PAPULAR			
subjects affected / exposed[164]	3 / 32 (9.38%)	1 / 30 (3.33%)	
occurrences (all)	3	2	
NAIL DISCOLOURATION			
subjects affected / exposed[165]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
SKIN FISSURES			
subjects affected / exposed[166]	1 / 32 (3.13%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
RASH PAPULAR			
subjects affected / exposed[167]	0 / 32 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
NAIL RIDGING			
subjects affected / exposed[168]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
ONYCHOMADESIS			
subjects affected / exposed[169]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
ERYTHEMA NODOSUM			
subjects affected / exposed[170]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
ALOPECIA			

subjects affected / exposed[171]	8 / 32 (25.00%)	10 / 30 (33.33%)	
occurrences (all)	8	10	
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed[172]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
ACUTE KIDNEY INJURY			
subjects affected / exposed[173]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
DYSURIA			
subjects affected / exposed[174]	3 / 32 (9.38%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Endocrine disorders			
HYPOTHYROIDISM			
subjects affected / exposed[175]	5 / 32 (15.63%)	3 / 30 (10.00%)	
occurrences (all)	5	3	
Musculoskeletal and connective tissue disorders			
MUSCLE SPASMS			
subjects affected / exposed[176]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
MUSCULAR WEAKNESS			
subjects affected / exposed[177]	2 / 32 (6.25%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
ARTHRALGIA			
subjects affected / exposed[178]	2 / 32 (6.25%)	4 / 30 (13.33%)	
occurrences (all)	2	4	
BONE PAIN			
subjects affected / exposed[179]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
NECK PAIN			
subjects affected / exposed[180]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
BACK PAIN			
subjects affected / exposed[181]	4 / 32 (12.50%)	4 / 30 (13.33%)	
occurrences (all)	6	5	
MUSCULOSKELETAL CHEST PAIN			

subjects affected / exposed[182]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
MYALGIA			
subjects affected / exposed[183]	2 / 32 (6.25%)	4 / 30 (13.33%)	
occurrences (all)	4	4	
JOINT SWELLING			
subjects affected / exposed[184]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
PAIN IN EXTREMITY			
subjects affected / exposed[185]	4 / 32 (12.50%)	3 / 30 (10.00%)	
occurrences (all)	5	5	
Infections and infestations			
SINUSITIS			
subjects affected / exposed[186]	2 / 32 (6.25%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
RASH PUSTULAR			
subjects affected / exposed[187]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
FURUNCLE			
subjects affected / exposed[188]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
INFLUENZA			
subjects affected / exposed[189]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
NASOPHARYNGITIS			
subjects affected / exposed[190]	1 / 32 (3.13%)	4 / 30 (13.33%)	
occurrences (all)	2	8	
PARONYCHIA			
subjects affected / exposed[191]	0 / 32 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
VAGINAL INFECTION			
subjects affected / exposed[192]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
LOCALISED INFECTION			
subjects affected / exposed[193]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	

UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed[194]	4 / 32 (12.50%)	5 / 30 (16.67%)	
occurrences (all)	5	5	
PNEUMONIA			
subjects affected / exposed[195]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
LYMPHANGITIS			
subjects affected / exposed[196]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
CYSTITIS			
subjects affected / exposed[197]	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
ORAL HERPES			
subjects affected / exposed[198]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
PHARYNGITIS			
subjects affected / exposed[199]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
CELLULITIS			
subjects affected / exposed[200]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	1	3	
NAIL INFECTION			
subjects affected / exposed[201]	1 / 32 (3.13%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
LARYNGITIS			
subjects affected / exposed[202]	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
IMPETIGO			
subjects affected / exposed[203]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
URINARY TRACT INFECTION			
subjects affected / exposed[204]	3 / 32 (9.38%)	7 / 30 (23.33%)	
occurrences (all)	4	9	
Metabolism and nutrition disorders			

DEHYDRATION			
subjects affected / exposed[205]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
HYPOMAGNESAEMIA			
subjects affected / exposed[206]	4 / 32 (12.50%)	3 / 30 (10.00%)	
occurrences (all)	5	3	
DECREASED APPETITE			
subjects affected / exposed[207]	4 / 32 (12.50%)	3 / 30 (10.00%)	
occurrences (all)	4	3	
HYPOPHOSPHATAEMIA			
subjects affected / exposed[208]	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
HYPOKALAEMIA			
subjects affected / exposed[209]	5 / 32 (15.63%)	3 / 30 (10.00%)	
occurrences (all)	5	4	
DIABETES MELLITUS			
subjects affected / exposed[210]	0 / 32 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	

Notes:

[53] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[54] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[56] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[57] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[59] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[60] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[62] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[63] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[64] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[65] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[67] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[68] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[69] - The number of subjects exposed to this adverse event is less than the total number of subjects

exposed for the reporting group. These numbers are expected to be equal.

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[72] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

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[73] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[74] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[75] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

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[76] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2017	The following updates were made: [1] An exploratory patient-reported outcome (PRO) objective for Cohort I was corrected to align with the procotol version 4; [2] The risks associated with atezolizumab were updated; [3] Information and guidance for anticipated overlapping AEs for cobimetinib and atezolizumab along with atezolizumab treatment interruption were added; [4] Guidelines for managing participants who experience diarrhea was revised to clarify the management of diarrhea for all participants; [5] Management guidelines for AEs were revised; [6] Guidelines for managing participants who experienced atezolizumab-associated AEs was added.
25 October 2018	The following updates were made: [1] Subsequent reviews of the triplet treatment combinations for Cohorts II and III were updated to take place as needed; [2] The flexible wording that paclitaxel "may also be considered an IMP in this study, depending on local legislation" was removed; [3] Guidelines for managing participants who experienced atezolizumab-associated AEs was revised; [4] The reporting of the term "sudden death" was updated; [5] AE reporting for hospitalization was updated; [6] The reporting timeframe for SAEs and AESIs was updated for Cohorts II and III; [7] Language was updated for clarity in various sections of the protocol; [8] The process for reviewing and handling protocol deviations was updated; [9] Clarification was made regarding the predose atezolizumab serum sampling times.
17 February 2021	The following updates were made: [1] The list of approved indications for atezolizumab was updated; [2] "Immune-related" was changed to "immune-mediated" when describing events associated with atezolizumab; [3] Immunosuppressive medications were removed from the prohibited therapy section and added to the cautionary therapy; [4] List of atezolizumab was updated; [5] Guidelines for management of atezolizumab-associated dermatologic AEs was revised; [6] Language was added for clarity in various sections of the protocol; [7] Appendix 10 (Anaphylaxis Precautions) was modified to remove the requirement for use of a tourniquet; [8] Appendix 11 has been revised to indicate that caution should be used when considering atezolizumab for participants who previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The sponsor decided to terminate this study.

Notes: