



Clinical trial results:

A Phase III, Open-Label, Multicenter, Two Arm, Randomized Study to Investigate the Efficacy and Safety of Cobimetinib Plus Atezolizumab Versus Pembrolizumab in Patients With Previously Untreated Advanced BRAF V600 Wild-Type Melanoma

Summary

EudraCT number	2016-004387-18
Trial protocol	DE NL BE HU PL GB ES GR FR IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	01 May 2020
First version publication date	01 May 2020

Trial information

Trial identification

Sponsor protocol code	CO39722
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03273153
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4070
Public contact	Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com
Scientific contact	Medical Communications, Hoffmann-La Roche, +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	Interim
Date of interim/final analysis	15 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy, safety, and pharmacokinetics of cobimetinib plus atezolizumab compared with pembrolizumab in treatment-naïve participants with advanced BRAFV600 wild-type melanoma.

Protection of trial subjects:

All participants were required to sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	France: 59
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Greece: 25
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Italy: 64
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Poland: 36
Country: Number of subjects enrolled	Russian Federation: 60
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	446
EEA total number of subjects	305

Notes:

Subjects enrolled per age group

In utero	0
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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)	202
From 65 to 84 years	237
85 years and over	7

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Treatment-naïve adult participants with advanced BRAFV600 wild-type melanoma.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab

Arm description:

Participants received 200 mg of intravenous (IV) pembrolizumab every 3 weeks (Q3W) until investigator-determined disease progression, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 200 mg of IV pembrolizumab once every 3 weeks.

Arm title	Cobimetinib and Atezolizumab
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Arm description:

Participants received 60 mg of cobimetinib by mouth (PO) on a 21 days on, 7 days off schedule (dosing on Days 1-21, followed by no dosing on Days 22-28) plus 840 mg of atezolizumab by IV infusion of Days 1 and 15 of each 28-day cycle.

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

Dosage and administration details:

Participants received 60 mg of oral cobimetinib once daily on a 21 days on, 7 days off schedule.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 840 mg of IV atezolizumab once every 2 weeks.

Number of subjects in period 1	Pembrolizumab	Cobimetinib and Atezolizumab
Started	224	222
Completed	0	0
Not completed	224	222
Adverse event, serious fatal	41	45
Consent withdrawn by subject	16	13
Remain on Study	161	159
Unspecified	-	1
Symptomatic Deterioration	-	1
Lost to follow-up	3	3
Protocol deviation	3	-

Baseline characteristics

Reporting groups

Reporting group title	Pembrolizumab
Reporting group description: Participants received 200 mg of intravenous (IV) pembrolizumab every 3 weeks (Q3W) until investigator-determined disease progression, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurred first.	
Reporting group title	Cobimetinib and Atezolizumab
Reporting group description: Participants received 60 mg of cobimetinib by mouth (PO) on a 21 days on, 7 days off schedule (dosing on Days 1-21, followed by no dosing on Days 22-28) plus 840 mg of atezolizumab by IV infusion of Days 1 and 15 of each 28-day cycle.	

Reporting group values	Pembrolizumab	Cobimetinib and Atezolizumab	Total
Number of subjects	224	222	446
Age categorical Units: Subjects			
Adults (18-64 years)	100	102	202
From 65-84 years	122	115	237
85 years and over	2	5	7
Age Continuous Units: Years			
arithmetic mean	63.5	63.6	
standard deviation	± 12.9	± 13.1	-
Sex: Female, Male Units:			
Female	83	93	176
Male	141	129	270
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	6	6	12
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	6	7
White	198	188	386
More than one race	0	0	0
Unknown or Not Reported	19	22	41
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	15	22
Not Hispanic or Latino	190	180	370
Unknown or Not Reported	27	27	54

End points

End points reporting groups

Reporting group title	Pembrolizumab
Reporting group description: Participants received 200 mg of intravenous (IV) pembrolizumab every 3 weeks (Q3W) until investigator-determined disease progression, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurred first.	
Reporting group title	Cobimetinib and Atezolizumab
Reporting group description: Participants received 60 mg of cobimetinib by mouth (PO) on a 21 days on, 7 days off schedule (dosing on Days 1-21, followed by no dosing on Days 22-28) plus 840 mg of atezolizumab by IV infusion of Days 1 and 15 of each 28-day cycle.	

Primary: Progression Free Survival (PFS) as Determined by the Independent Review Committee (IRC)

End point title	Progression Free Survival (PFS) as Determined by the Independent Review Committee (IRC)
End point description: PFS is defined as the time from randomization to the first occurrence of disease progression, as determined by an IRC according to RECIST v1.1, or death from any cause, whichever occurs first. Progressive disease (PD) for target lesion: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm. PD for non-target lesion: Unequivocal progression of existing non-target lesions. Tumor assessments, including contrast-enhanced CT or MRI scans, will be performed every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter, until confirmed disease progression or loss of clinical benefit, withdrawal of consent, study termination by the Sponsor or death, whichever occurs first.	
End point type	Primary
End point timeframe: Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter	

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	222		
Units: Months				
median (confidence interval 95%)	5.7 (3.7 to 9.6)	5.5 (3.8 to 7.2)		

Statistical analyses

Statistical analysis title	PFS
Comparison groups	Pembrolizumab v Cobimetinib and Atezolizumab

Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2954
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.5

Secondary: PFS as Determined by the Investigator

End point title	PFS as Determined by the Investigator
End point description:	
PFS is defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Progressive disease (PD) for target lesion: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm. PD for non-target lesion: Unequivocal progression of existing non-target lesions.	
End point type	Secondary
End point timeframe:	
Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter	

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	222		
Units: Months				
median (confidence interval 95%)	7.2 (3.8 to 10.1)	5.6 (3.9 to 6.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response as Determined by the Investigator

End point title	Objective Response as Determined by the Investigator
End point description:	
Objective response rate is defined as the percentage of participants with a complete response (CR) or a partial response (PR) on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator through the use of RECIST v1.1. For target lesion, CR: the disappearance of all target lesions, any pathological lymph nodes must have a reduction in short axis to < 10 mm. PR: at least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of	

diameters, in the absence of CR. For non-target lesion, CR: the disappearance of all non-target lesions and (if applicable) normalization of tumor marker level, all lymph nodes must be non-pathological in size (<10 mm short axis).

End point type	Secondary
End point timeframe:	
Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter	

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	222		
Units: Percentage of Participants				
number (confidence interval 95%)	36.7 (30.29 to 43.38)	27.9 (22.13 to 34.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response as Determined by IRC

End point title	Objective Response as Determined by IRC
End point description:	
Objective response, defined as a complete response or partial response on two consecutive occasions ≥4 weeks apart, as determined by IRC according to RECIST v1.1	
End point type	Secondary
End point timeframe:	
Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter	

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	204		
Units: Percentage of Participants				
number (confidence interval 95%)	31.6 (25.27 to 38.38)	26.0 (20.11 to 32.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
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End point description:

DCR is defined as the proportion of participants with a complete response, a partial response, or stable disease at 16 weeks. For target lesion, CR: the disappearance of all target lesions, any pathological lymph nodes must have a reduction in short axis to <10 mm. PR: at least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. For non-target lesion, CR: the disappearance of all non-target lesions and (if applicable) normalization of tumor marker level, all lymph nodes must be non-pathological in size (<10 mm short axis). Stable disease (SD): neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD.

End point type	Secondary
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End point timeframe:

Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	222		
Units: Percentage of Participants				
number (confidence interval 95%)				
Investigator-assessed	49.8 (43.00 to 56.56)	46.8 (40.14 to 53.64)		
IRC-assessed (n= 206, 204)	44.2 (37.28 to 51.24)	45.6 (38.62 to 52.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

OS is defined as the time from randomization to death from any cause.

End point type	Secondary
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End point timeframe:

Up to 7 years

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224 ^[1]	222 ^[2]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (13.0 to 9999)		

Notes:

[1] - 9999 = value not available due to insufficient number of participants with event

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of objective response determined by the IRC

End point title	Duration of objective response determined by the IRC
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End point description:

Duration of objective response, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by an IRC according to RECIST v1.1, or death from any cause, whichever occurs first.

End point type	Secondary
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End point timeframe:

Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65 ^[3]	53 ^[4]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9.2 to 9999)		

Notes:

[3] - 9999 = Values are not estimable due to an insufficient number of participants with the event.

[4] - 9999 = Values are not estimable due to an insufficient number of participants with the event.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response determined by the Investigator

End point title	Duration of Objective Response determined by the Investigator
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End point description:

Duration of objective response is defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator through use of RECIST v1.1, or death from any cause, whichever occurs first.

End point type	Secondary
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End point timeframe:

Every 8 weeks (wks) from Day (D) 1 of Cycle (C) 1 through 80 wks and then every 12 wks thereafter

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81 ^[5]	62 ^[6]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9.2 to 9999)		

Notes:

[5] - 9999 = value not available due to insufficient number of participants with event

[6] - 9999 = value not available due to insufficient number of participants with event

Statistical analyses

No statistical analyses for this end point

Secondary: Two-year Landmark Survival

End point title	Two-year Landmark Survival
End point description:	Two-year landmark survival is defined as survival at 2 years.
End point type	Secondary
End point timeframe:	At 2 years

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[7]	0 ^[8]		
Units: None				
number (not applicable)				

Notes:

[7] - Timeframe for endpoint has not yet been reached.

[8] - Timeframe for endpoint has not yet been reached.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-related Quality of Life (HRQoL) Scores

End point title	Change From Baseline in Health-related Quality of Life (HRQoL) Scores
End point description:	HRQoL scores are assessed through global health status (GHS)/ quality of life (QoL) subscale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C30). These are based on questions 29 and 30 of the EORTC QLQ-C30. These questions on global health status/QoL scale are coded on 7-point scale (1=very poor to 7=excellent). Raw scores will be linearly transformed to obtain the score ranging from 0 to 100, where higher score represents a higher ("better") level of functioning.
End point type	Secondary
End point timeframe:	Up to 7 years

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174 ^[9]	160 ^[10]		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Baseline value	73.27 (± 20.41)	73.85 (± 19.73)		
Week 4	-2.99 (± 17.05)	-9.14 (± 20.83)		
Week 8	-3.15 (± 18.67)	-5.21 (± 18.18)		
Week 12	-1.77 (± 19.93)	-7.65 (± 21.20)		
Week 16	1.16 (± 15.02)	-6.44 (± 20.58)		
Week 20	1.69 (± 17.50)	-6.31 (± 19.17)		
Week 24	-1.84 (± 19.82)	-2.49 (± 15.98)		
Week 28	2.46 (± 19.07)	-3.86 (± 19.10)		
Week 32	-0.88 (± 22.41)	-4.66 (± 20.94)		
Week 36	4.17 (± 20.56)	-6.00 (± 18.24)		
Week 40	7.22 (± 19.38)	-4.63 (± 21.62)		
Week 44	0.46 (± 19.27)	1.67 (± 12.91)		
Week 48	7.64 (± 13.04)	0.00 (± 15.96)		
Week 52	1.67 (± 12.36)	8.33 (± 15.21)		
Week 56	-11.11 (± 17.21)	-2.08 (± 4.17)		
Week 60	-8.33 (± 11.79)	-4.17 (± 5.89)		
Week 64	33.33 (± 9999)	9999 (± 9999)		
Treatment Discontinuation	-6.05 (± 22.53)	-14.42 (± 25.68)		
Follow-up 4	-7.64 (± 14.85)	-2.27 (± 18.67)		
Follow-up 8	-14.25 (± 21.96)	-14.10 (± 24.15)		
Follow-up 12	-21.38 (± 24.34)	-24.31 (± 28.08)		
Follow-up 16	-13.73 (± 19.53)	-23.61 (± 23.26)		
Follow-up 20	-20.83 (± 26.53)	-8.33 (± 12.91)		
Follow-up 24	-17.71 (± 29.36)	-10.00 (± 14.91)		
Follow-up 28	-27.78 (± 22.15)	-16.67 (± 23.57)		

Notes:

[9] - 9999 = value not available

[10] - 9999 = value not available

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)
End point description: An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events.	
End point type	Secondary
End point timeframe: Up to 7 years	

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	220		
Units: Number of Participants	191	218		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Vital Signs

End point title	Number of Participants With Abnormal Vital Signs
End point description: Vital signs will include temperature pulse rate, respiratory rate, and systolic and diastolic blood pressure.	
End point type	Secondary
End point timeframe: Up to 7 years	

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[11]	0 ^[12]		
Units: Number of Participants				
number (not applicable)				

Notes:

[11] - Values not available at the time of primary results reporting.

[12] - Values not available at the time of primary results reporting.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Laboratory Abnormalities

End point title	Number of Participants With Laboratory Abnormalities
End point description:	Participants with laboratory abnormalities (values outside of a defined range) are reported.
End point type	Secondary
End point timeframe:	
Up to 7 years	

End point values	Pembrolizumab	Cobimetinib and Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	220		
Units: Number of Participants				
SGPT/ALT	1	1		
Amylase (n= 201, 204)	4	5		
SGOT/AST (n= 215, 220)	0	2		
Calcium	0	1		
Creatine Kinase (n= 215, 220)	1	17		
Creatinine	1	4		
Glucose (n= 210, 218)	8	13		
Triacylglycerol Lipase (n= 197, 200)	8	10		
Magnesium (n= 215, 217)	3	2		
Phosphorus (n= 216, 217)	6	10		
Potassium	1	6		
Sodium	2	4		
Uric Acid (n= 179, 188)	36	30		
Hemoglobin	2	2		
Lymphocytes Abs (n= 173, 178)	6	15		
Neutrophils, Total, Abs (n= 174, 179)	0	1		
Total Leukocyte Count	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Cobimetinib

End point title	Plasma Concentration of Cobimetinib ^[13]
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End point description:

Plasma concentration of cobimetinib at specified time points will be reported.

End point type	Secondary
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End point timeframe:

Days 1 and 15 of Cycle 1

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 endpoint is specific to the reported arm.

End point values	Cobimetinib and Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[14]			
Units: ng/mL				
arithmetic mean (standard deviation)	()			

Notes:

[14] - PK parameters will be reported with final results.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Atezolizumab

End point title	Serum Concentration of Atezolizumab ^[15]
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End point description:

Serum concentration of atezolizumab at specified time points will be reported.

End point type	Secondary
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End point timeframe:

Day 1 of Cycle 1, 2, 3 and 30 days after treatment discontinuation

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 endpoint is specific to the reported arm.

End point values	Cobimetinib and Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[16]			
Units: none				
number (not applicable)				

Notes:

[16] - PK parameters will be reported with final results.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-drug Antibodies (ADAs)

End point title	Percentage of Participants with Anti-drug Antibodies (ADAs) ^[17]
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End point description:

Participants with ADAs during the study relative to the prevalence of ADAs at baseline will be reported.

End point type	Secondary
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End point timeframe:

Day 1 of Cycle 1, 2, 3 and 30 days after treatment discontinuation

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is specific to the reported arm.

End point values	Cobimetinib and Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[18]			
Units: None				
number (not applicable)				

Notes:

[18] - PD parameters will be reported with final results.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For up to 135 days after the last dose of study drug, or until a new systemic anti-cancer therapy was initiated, whichever occurred first.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Cobimetinib and Atezolizumab
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Reporting group description:

Participants received 60 mg of cobimetinib by mouth (PO) on a 21 days on, 7 days off schedule (dosing on Days 1-21, followed by no dosing on Days 22-28) plus 840 mg of atezolizumab by IV infusion of Days 1 and 15 of each 28-day cycle.

Reporting group title	Pembrolizumab
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Reporting group description:

Participants received 200 mg of IV pembrolizumab every 3 weeks (Q3W) until investigator-determined disease progression, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurred first.

Serious adverse events	Cobimetinib and Atezolizumab	Pembrolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	97 / 220 (44.09%)	45 / 216 (20.83%)	
number of deaths (all causes)	45	42	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 220 (0.45%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	12 / 220 (5.45%)	2 / 216 (0.93%)	
occurrences causally related to treatment / all	0 / 12	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	4 / 220 (1.82%)	3 / 216 (1.39%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	3 / 220 (1.36%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 220 (0.45%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest pain			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	45 / 220 (20.45%)	42 / 216 (19.44%)	
occurrences causally related to treatment / all	1 / 45	0 / 42	
deaths causally related to treatment / all	1 / 45	0 / 42	
Malaise			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 220 (0.91%)	4 / 216 (1.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 220 (1.36%)	2 / 216 (0.93%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemoptysis			
subjects affected / exposed	2 / 220 (0.91%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 220 (0.91%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 220 (0.91%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 220 (0.91%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 220 (0.91%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Alanine aminotransferase increased subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction subjects affected / exposed	3 / 220 (1.36%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 220 (1.36%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 220 (0.45%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Ischaemic stroke			
subjects affected / exposed	3 / 220 (1.36%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 220 (0.45%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 220 (0.91%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune encephalopathy			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune neuropathy			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis autoimmune			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			

subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 220 (0.91%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (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	9 / 220 (4.09%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 220 (2.27%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 220 (0.45%)	3 / 216 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 220 (0.91%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	2 / 220 (0.91%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 220 (0.91%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			

subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis mesenteric vessel			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic pain			

subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 220 (1.82%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis acneiform			
subjects affected / exposed	3 / 220 (1.36%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative generalised			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pemphigoid			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash macular			

subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 220 (1.36%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	2 / 220 (0.91%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder perforation			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dupuytren's contracture			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleroderma			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	6 / 220 (2.73%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	3 / 220 (1.36%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 220 (0.91%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 220 (0.45%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	2 / 220 (0.91%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryocystitis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spleen tuberculosis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection viral			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic shock syndrome			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			

subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 220 (0.45%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 220 (0.45%)	0 / 216 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 220 (0.00%)	1 / 216 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cobimetinib and Atezolizumab	Pembrolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	209 / 220 (95.00%)	162 / 216 (75.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	26 / 220 (11.82%)	14 / 216 (6.48%)	
occurrences (all)	36	14	
Amylase increased			
subjects affected / exposed	14 / 220 (6.36%)	7 / 216 (3.24%)	
occurrences (all)	23	8	
Aspartate aminotransferase increased			
subjects affected / exposed	38 / 220 (17.27%)	14 / 216 (6.48%)	
occurrences (all)	50	14	
Blood creatine phosphokinase increased			
subjects affected / exposed	76 / 220 (34.55%)	9 / 216 (4.17%)	
occurrences (all)	108	12	
Blood lactate dehydrogenase increased			
subjects affected / exposed	12 / 220 (5.45%)	4 / 216 (1.85%)	
occurrences (all)	14	4	
Lipase increased			
subjects affected / exposed	22 / 220 (10.00%)	12 / 216 (5.56%)	
occurrences (all)	39	14	
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 220 (9.55%)	11 / 216 (5.09%)	
occurrences (all)	26	15	
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 220 (6.36%)	7 / 216 (3.24%)	
occurrences (all)	18	10	
Headache			
subjects affected / exposed	24 / 220 (10.91%)	17 / 216 (7.87%)	
occurrences (all)	30	18	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	30 / 220 (13.64%)	12 / 216 (5.56%)	
occurrences (all)	41	12	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	55 / 220 (25.00%)	39 / 216 (18.06%)	
occurrences (all)	76	43	
Fatigue			
subjects affected / exposed	42 / 220 (19.09%)	41 / 216 (18.98%)	
occurrences (all)	61	53	
Oedema peripheral			
subjects affected / exposed	45 / 220 (20.45%)	13 / 216 (6.02%)	
occurrences (all)	63	13	
Pyrexia			
subjects affected / exposed	62 / 220 (28.18%)	15 / 216 (6.94%)	
occurrences (all)	82	16	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	22 / 220 (10.00%)	13 / 216 (6.02%)	
occurrences (all)	26	16	
Constipation			
subjects affected / exposed	30 / 220 (13.64%)	18 / 216 (8.33%)	
occurrences (all)	33	21	
Diarrhoea			
subjects affected / exposed	118 / 220 (53.64%)	35 / 216 (16.20%)	
occurrences (all)	246	44	
Dry mouth			
subjects affected / exposed	16 / 220 (7.27%)	6 / 216 (2.78%)	
occurrences (all)	17	6	
Nausea			
subjects affected / exposed	53 / 220 (24.09%)	26 / 216 (12.04%)	
occurrences (all)	59	30	
Stomatitis			
subjects affected / exposed	12 / 220 (5.45%)	3 / 216 (1.39%)	
occurrences (all)	16	4	

Vomiting subjects affected / exposed occurrences (all)	39 / 220 (17.73%) 49	15 / 216 (6.94%) 15	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	 17 / 220 (7.73%) 20 15 / 220 (6.82%) 21	 18 / 216 (8.33%) 20 16 / 216 (7.41%) 16	
Skin and subcutaneous tissue disorders Dermatitis acneiform subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Pruritis subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all)	 50 / 220 (22.73%) 62 14 / 220 (6.36%) 17 12 / 220 (5.45%) 13 39 / 220 (17.73%) 48 89 / 220 (40.45%) 132 26 / 220 (11.82%) 36	 3 / 216 (1.39%) 3 11 / 216 (5.09%) 12 6 / 216 (2.78%) 6 30 / 216 (13.89%) 37 25 / 216 (11.57%) 34 5 / 216 (2.31%) 6	
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all)	 7 / 220 (3.18%) 7 13 / 220 (5.91%) 14	 19 / 216 (8.80%) 19 15 / 216 (6.94%) 15	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 220 (6.36%)	24 / 216 (11.11%)	
occurrences (all)	15	30	
Back pain			
subjects affected / exposed	12 / 220 (5.45%)	19 / 216 (8.80%)	
occurrences (all)	15	19	
Myalgia			
subjects affected / exposed	13 / 220 (5.91%)	10 / 216 (4.63%)	
occurrences (all)	15	10	
Pain in extremity			
subjects affected / exposed	11 / 220 (5.00%)	7 / 216 (3.24%)	
occurrences (all)	11	8	
Infections and infestations			
Folliculitis			
subjects affected / exposed	13 / 220 (5.91%)	1 / 216 (0.46%)	
occurrences (all)	20	1	
Rash pustular			
subjects affected / exposed	12 / 220 (5.45%)	1 / 216 (0.46%)	
occurrences (all)	12	1	
Urinary tract infection			
subjects affected / exposed	12 / 220 (5.45%)	2 / 216 (0.93%)	
occurrences (all)	14	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	30 / 220 (13.64%)	16 / 216 (7.41%)	
occurrences (all)	33	18	
Hyperglycaemia			
subjects affected / exposed	16 / 220 (7.27%)	9 / 216 (4.17%)	
occurrences (all)	20	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2017	Updated eligibility criteria; changed pembrolizumab dosing per United Surgical Partners International (USPI)
12 March 2018	Added IRB assessment for secondary endpoints ORR and DOR; updated eligibility criteria
19 September 2018	Updated eligibility criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported