Clinical trial results:
A Phase III, Double-blinded, Randomized, Placebo-controlled Study of Atezolizumab Plus Cobimetinib and Vemurafenib Versus Placebo Plus Cobimetinib and Vemurafenib in Previously Untreated BRAFV600 Mutation-positive Patients With Unresectable Locally Advanced or Metastatic Melanoma

Summary

EudraCT number	2016-002482-54
Trial protocol	ES HU DE AT GB NL PL PT GR FR BE IT
Global end of trial date	01 July 2024

Results information

Result version number	v1 (current)
This version publication date	12 July 2025
First version publication date	12 July 2025

Trial information

Trial identification

Sponsor protocol code	CO39262

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02908672
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4058
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	01 July 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to evaluate the efficacy of atezolizumab plus cobimetinib plus vemurafenib (atezo + cobi + vem) compared with placebo plus cobimetinib plus vemurafenib (pbo + cobi + vem) in participants with previously untreated, B-Raf proto-oncogene serine/threonine kinase (BRAF) V600 mutation-positive, metastatic, or unresectable locally advanced melanoma.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	85 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Brazil: 45
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	New Zealand: 10
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 72
Country: Number of subjects enrolled	Greece: 27
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Italy: 67
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 36
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Russian Federation: 73
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	United Kingdom: 14

Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	514
EEA total number of subjects	302

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)	394
From 65 to 84 years	118
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 514 participants with BRAFV600 mutation positive metastatic or unresectable locally advanced melanoma took part in the study at 112 investigational sites in 20 countries from 13 January 2017 to 01 Jul 2024.
Study was closed early by sponsor due to slower-than-anticipated OS event accumulation, & hence was considered to be completed.

Pre-assignment

Screening details:

Participants received either Pbo+Cobi+Vem or Atezo+Cobi+Vem. 26 participants in pbo+cobi+vem arm were included for safety analysis (22 in atezo+cobi+vem arm stopped run-in treatment & 4 completed the run-in treatment but none of them received atezo). 2 participants in pbo+cobi+vem arm received atezo & were included in atezo+cobi+vem arm for safety.

Period 1

Period 1 title	Run-in Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Pbo + Cobi + Vem

Arm description:

Participants received vemurafenib, 960 milligrams (mg) (four, 240 mg tablets), orally (PO), twice a day (BID) along with cobimetinib, 60 mg (three, 20 mg tablets) PO, once a day (QD) on Days 1 to 21 only followed by vemurafenib 960 mg (four, 240 mg tablets), PO, BID on Days 22 to 28 during the 28 day run-in period. During triple combination period (Cycle 1 onwards), participants received atezolizumab matching placebo as intravenous (IV) infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21 and vemurafenib 960 mg (four, 240 mg tablets) PO, BID on Days 1 to 28. Study treatment was continued until investigator determined disease progression (PD), death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	RO5514041
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib, 60 mg tablets, PO, QD administered on Days 1 to 21 of each 28-day cycle during the Run-in Period.

Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	RO5185426
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vemurafenib, 960 mg tablets, PO BID administered on Days 1 to 28 of each 28-day cycle during the Run-in Period.

Arm title	Arm B: Atezo + Cobi + Vem

Arm description:

Participants received vemurafenib, 960 mg (four, 240 mg tablets) PO, BID along with cobimetinib 60 mg

(three, 20 mg tablets) PO, QD on Days 1 to 21 only followed by vemurafenib 720 mg (three, 240 mg tablets) PO, BID and vemurafenib matching placebo, PO, BID on Days 22 to 28 during the 28 day run-in period. During triple combination period (Cycle 1 onwards), participants received atezolizumab 840 mg as IV infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21, vemurafenib 720 mg (three, 240 mg tablets) PO BID on Days 1 to 28, and vemurafenib placebo (1 tablet) PO BID on Days 1 to 28. Study treatment was continued until investigator determined PD, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	RO5185426
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vemurafenib, 960 mg tablets, PO, BID administered on Days 1 to 21, and 720 mg tablets, PO, BID administered on Days 22-28 of each 28-day cycle during the Run-in Period.

Investigational medicinal product name	Vemurafenib placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vemurafenib matching placebo, PO, BID administered on Days 22 to 28 of each 28-day cycle during the Run-in period.

Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	RO5514041
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib, 60 mg tablets, PO, QD administered on Days 1 to 21 of each 28-day cycle during the Run-in Period.

Number of subjects in period 1	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem
Started	258	256
Completed	234	234
Not completed	24	22
Consent withdrawn by subject	3	9
Study Ended by Sponsor	5	1
Death	12	10
Reason Not Specified	2	-
Lost to follow-up	1	1
Protocol deviation	1	1

Period 2

Period 2 title	Triple Combination Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Pbo + Cobi + Vem

Arm description:

Participants received vemurafenib, 960 mg (four, 240 mg tablets), PO, BID along with cobimetinib, 60 mg (three, 20 mg tablets) PO, QD on Days 1 to 21 only followed by vemurafenib 960 mg (four, 240 mg tablets), PO, BID on Days 22 to 28 during the 28 day run-in period. During triple combination period (Cycle 1 onwards), participants received atezolizumab matching placebo as IV infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21 and vemurafenib 960 mg (four, 240 mg tablets) PO, BID on Days 1 to 28. Study treatment was continued until investigator determined PD, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab matching placebo as IV infusion administered on Days 1 and 15 of each 28-day cycle during the Triple Combination Period.

Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	RO5185426
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vemurafenib 960 mg, PO, BID administered on Days 1 to 28 of each 28-day cycle during the Triple Combination Period.

Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	RO5514041
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib, 60 mg tablets, PO, QD administered on Days 1 to 21 of each 28-day cycle during the Triple Combination Period.

Arm title	Arm B: Atezo + Cobi + Vem

Arm description:

Participants received vemurafenib, 960 mg (four, 240 mg tablets) PO, BID along with cobimetinib 60 mg (three, 20 mg tablets) PO, QD on Days 1 to 21 only followed by vemurafenib 720 mg (three, 240 mg tablets) PO, BID and vemurafenib matching placebo, PO, BID on Days 22 to 28 during the 28 day run-in period. During triple combination period (Cycle 1 onwards), participants received atezolizumab 840 mg as IV infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21, vemurafenib 720 mg (three, 240 mg tablets) PO BID on Days 1 to 28, and vemurafenib placebo (1 tablet) PO BID on Days 1 to 28. Study treatment was continued until investigator determined PD, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.

Arm type	Experimental

Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	RO5514041
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib, 60 mg tablets, PO, QD administered on Days 1 to 21 of each 28-day cycle during the Triple Combination Period.

Investigational medicinal product name	Vemurafenib Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vemurafenib matching placebo, PO, BID administered on Days 1 to 21 of each 28-day cycle during the Triple Combination Period.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	RO5541267
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab, 840 mg, IV infusion was administered on Days 1 and 15 of each 28-day cycle during the Triple Combination Period.

Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	RO5185426
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vemurafenib, 720 mg tablets, PO, BID administered on days 1-28 of each 28-day cycle during the Triple Combination Period.

Number of subjects in period 2[1]	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem
Started	231	230
Completed	0	0
Not completed	231	230
Physician decision	1	1
Consent withdrawn by subject	13	16
Study Ended by Sponsor	61	77
Death	150	127
Reason Not Specified	-	1
Lost to follow-up	6	8

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 7 participants completed run-in but did not receive Pbo or Atezo after completing run-in. Hence, they are not presented here.

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Pbo + Cobi + Vem
Reporting group description:	
Participants received vemurafenib, 960 milligrams (mg) (four, 240 mg tablets), orally (PO), twice a day (BID) along with cobimetinib, 60 mg (three, 20 mg tablets) PO, once a day (QD) on Days 1 to 21 only followed by vemurafenib 960 mg (four, 240 mg tablets), PO, BID on Days 22 to 28 during the 28 day run-in period. During triple combination period (Cycle 1 onwards), participants received atezolizumab matching placebo as intravenous (IV) infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21 and vemurafenib 960 mg (four, 240 mg tablets) PO, BID on Days 1 to 28. Study treatment was continued until investigator determined disease progression (PD), death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.	
Reporting group title	Arm B: Atezo + Cobi + Vem
Reporting group description:	
Participants received vemurafenib, 960 mg (four, 240 mg tablets) PO, BID along with cobimetinib 60 mg (three, 20 mg tablets) PO, QD on Days 1 to 21 only followed by vemurafenib 720 mg (three, 240 mg tablets) PO, BID and vemurafenib matching placebo, PO, BID on Days 22 to 28 during the 28 day run-in period. During triple combination period (Cycle 1 onwards), participants received atezolizumab 840 mg as IV infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21, vemurafenib 720 mg (three, 240 mg tablets) PO BID on Days 1 to 28, and vemurafenib placebo (1 tablet) PO BID on Days 1 to 28. Study treatment was continued until investigator determined PD, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.	

Reporting group values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem	Total
Number of subjects	258	256	514
Age Categorical Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	199	195	394
>=65 years	59	61	120
Age Continuous Units: years			
arithmetic mean	53.2	54.0	
standard deviation	± 14.1	± 14.2	-
Sex: Female, Male Units: participants			
Female	109	106	215
Male	149	150	299
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	20	27	47
Not Hispanic or Latino	225	223	448
Unknown or Not Reported	13	6	19
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	4	7	11
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	0	1	1
White	246	243	489
More than one race	0	0	0

Unknown or Not Reported	6	4	10

End points reporting groups

Reporting group title	Arm A: Pbo + Cobi + Vem

Reporting group description:

Participants received vemurafenib, 960 milligrams (mg) (four, 240 mg tablets), orally (PO), twice a day (BID) along with cobimetinib, 60 mg (three, 20 mg tablets) PO, once a day (QD) on Days 1 to 21 only followed by vemurafenib 960 mg (four, 240 mg tablets), PO, BID on Days 22 to 28 during the 28 day run-in period. During triple combination period (Cycle 1 onwards), participants received atezolizumab matching placebo as intravenous (IV) infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21 and vemurafenib 960 mg (four, 240 mg tablets) PO, BID on Days 1 to 28. Study treatment was continued until investigator determined disease progression (PD), death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.

Reporting group title	Arm B: Atezo + Cobi + Vem

Reporting group description:

Participants received vemurafenib, 960 mg (four, 240 mg tablets) PO, BID along with cobimetinib 60 mg (three, 20 mg tablets) PO, QD on Days 1 to 21 only followed by vemurafenib 720 mg (three, 240 mg tablets) PO, BID and vemurafenib matching placebo, PO, BID on Days 22 to 28 during the 28 day run-in period. During triple combination period (Cycle 1 onwards), participants received atezolizumab 840 mg as IV infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21, vemurafenib 720 mg (three, 240 mg tablets) PO BID on Days 1 to 28, and vemurafenib placebo (1 tablet) PO BID on Days 1 to 28. Study treatment was continued until investigator determined PD, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.

Reporting group title	Arm A: Pbo + Cobi + Vem

Reporting group description:

Participants received vemurafenib, 960 mg (four, 240 mg tablets), PO, BID along with cobimetinib, 60 mg (three, 20 mg tablets) PO, QD on Days 1 to 21 only followed by vemurafenib 960 mg (four, 240 mg tablets), PO, BID on Days 22 to 28 during the 28 day run-in period. During triple combination period (Cycle 1 onwards), participants received atezolizumab matching placebo as IV infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21 and vemurafenib 960 mg (four, 240 mg tablets) PO, BID on Days 1 to 28. Study treatment was continued until investigator determined PD, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.

Reporting group title	Arm B: Atezo + Cobi + Vem

Reporting group description:

Participants received vemurafenib, 960 mg (four, 240 mg tablets) PO, BID along with cobimetinib 60 mg (three, 20 mg tablets) PO, QD on Days 1 to 21 only followed by vemurafenib 720 mg (three, 240 mg tablets) PO, BID and vemurafenib matching placebo, PO, BID on Days 22 to 28 during the 28 day run-in period. During triple combination period (Cycle 1 onwards), participants received atezolizumab 840 mg as IV infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21, vemurafenib 720 mg (three, 240 mg tablets) PO BID on Days 1 to 28, and vemurafenib placebo (1 tablet) PO BID on Days 1 to 28. Study treatment was continued until investigator determined PD, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.

Subject analysis set title	Arm A: Pbo + Cobi + Vem
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received vemurafenib, 960 mg (four, 240 mg tablets), PO, BID along with cobimetinib, 60 mg (three, 20 mg tablets) PO, QD on Days 1 to 21 only followed by vemurafenib 960 mg (four, 240 mg tablets), PO, BID on Days 22 to 28 during the 28 day run-in period. During triple combination period (Cycle 1 onwards), participants received atezolizumab matching placebo as IV infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21 and vemurafenib 960 mg (four, 240 mg tablets) PO, BID on Days 1 to 28. Study treatment was continued until investigator determined PD, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.

Subject analysis set title	Arm B: Atezo + Cobi + Vem
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received vemurafenib, 960 mg (four, 240 mg tablets) PO, BID along with cobimetinib 60 mg (three, 20 mg tablets) PO, QD on Days 1 to 21 only followed by vemurafenib 720 mg (three, 240 mg tablets) PO, BID and vemurafenib matching placebo, PO, BID on Days 22 to 28 during the 28 day run-in period. During triple combination period (Cycle 1 onwards), participants received atezolizumab 840 mg as IV infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21, vemurafenib 720 mg (three, 240 mg tablets) PO BID on Days 1 to 28, and vemurafenib placebo (1

tablet) PO BID on Days 1 to 28. Study treatment was continued until investigator determined PD, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.

Primary: Progression-Free Survival (PFS), as Determined by Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

End point title	Progression-Free Survival (PFS), as Determined by Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

End point description:

PFS was defined as the time from randomization to the first occurrence of PD, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurred first. PD was defined as at least a 20% increase in the sum of diameters (SOD) of target lesions, taking as reference smallest sum on study, including baseline. In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of at least 5 millimeters (mm). ITT population included all randomized participants, whether or not study treatment was received.

End point type	Primary

End point timeframe:

Baseline up to PD or death due to any cause, whichever occurred first (up to approximately 33 months)

End point values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	256		
Units: months				
median (confidence interval 95%)	10.6 (9.3 to 12.7)	15.1 (11.4 to 18.4)		

Statistical analyses

Statistical analysis title	Pbo + Cobi + Vem vs Atezo + Cobi + Vem
Statistical analysis description:	
Stratified Hazard Ratio	
Comparison groups	Arm B: Atezo + Cobi + Vem v Arm A: Pbo + Cobi + Vem
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0224
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.97

Secondary: PFS as Determined by Independent Review Committee (IRC) Using RECIST v1.1

End point title	PFS as Determined by Independent Review Committee (IRC) Using RECIST v1.1

End point description:

PFS was defined as the time from randomization to the first occurrence of disease progression, as determined by the IRC according to RECIST v1.1, or death from any cause, whichever occurred first. PD was defined as at least a 20% increase in the SOD of target lesions, taking as reference smallest sum on study, including baseline. In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of at least 5 mm. ITT population included all randomized participants, whether or not study treatment was received.

End point type	Secondary

End point timeframe:

Baseline up to PD or death due to any cause, whichever occurred first (up to approximately 33 months)

End point values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	256		
Units: months				
median (confidence interval 95%)	12.3 (10.8 to 14.7)	16.1 (11.3 to 18.5)		

Statistical analyses

Statistical analysis title	Pbo + Cobi + Vem vs Atezo + Cobi + Vem
Comparison groups	Arm A: Pbo + Cobi + Vem v Arm B: Atezo + Cobi + Vem
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1607
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.07

Secondary: Percentage of Participants With Objective Response (OR), as Determined by Investigator Using RECIST V1.1

End point title	Percentage of Participants With Objective Response (OR), as Determined by Investigator Using RECIST V1.1

End point description:

OR rate was defined as percentage of participants with partial response (PR) or complete response (CR) on 2 consecutive occasions ≥ 4 weeks apart as determined by the investigator using RECIST v.1.1. CR

was defined as the disappearance of all target lesions or any pathological lymph nodes (whether target or non-target) having a reduction in short axis to <10 mm. PR was defined as at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD. ITT population included all randomized participants, whether or not study treatment was received. Only participants with measurable disease at baseline were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to PD or death due to any cause, whichever occurred first (up to approximately 56 months)

End point values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	255		
Units: percentage of participants				
number (not applicable)	65.0	66.7		

Statistical analyses

Statistical analysis title	Pbo + Cobi + Vem vs Atezo + Cobi + Vem
Comparison groups	Arm A: Pbo + Cobi + Vem v Arm B: Atezo + Cobi + Vem
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6997
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rate
Point estimate	1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	10.15

Secondary: Duration of Response (DOR), as Determined by Investigator Using RECIST v1.1

End point title	Duration of Response (DOR), as Determined by Investigator Using RECIST v1.1

End point description:

DOR was defined as the time from the first occurrence of a documented OR to PD, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurred first. PD was defined as at least a 20% increase in the SOD of target lesions, taking as reference smallest sum on study, including baseline. In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of at least 5 mm. CR was defined as the disappearance of all target lesions or any pathological lymph nodes (whether target or non-target) having a reduction in short axis to <10 mm. PR was defined as at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD. ITT population included all randomized participants, whether or not study treatment was received. Only participants with measurable disease at baseline were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to PD or death due to any cause, whichever occurred first (up to approximately 56 months)

End point values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	255		
Units: months				
median (confidence interval 95%)	12.6 (10.5 to 16.7)	21.0 (16.6 to 32.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death from any cause. ITT population included all randomized participants, whether or not study treatment was received.

End point type	Secondary

End point timeframe:

Baseline up to death due to any cause (up to approximately 85 months)

End point values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	256		
Units: months				
median (confidence interval 95%)	25.8 (22.0 to 34.6)	39.0 (29.9 to 55.3)		

Statistical analyses

Statistical analysis title	Pbo + Cobi + Vem vs Atezo + Cobi + Vem
Comparison groups	Arm A: Pbo + Cobi + Vem v Arm B: Atezo + Cobi + Vem
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1191
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.05

Secondary: Percentage of Participants Who Have Survived at 2 Years

End point title	Percentage of Participants Who Have Survived at 2 Years

End point description:

Percentage of participants with OS which was defined as the time from randomization to death from any cause. The Kaplan-Meier approach was used to estimate 2-year landmark survival rate. The 95% CI of landmark survival rate was calculated using the standard error derived from Greenwood's formula. ITT population included all randomized participants, whether or not study treatment was received.

End point type	Secondary

End point timeframe:

2 years

End point values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	256		
Units: percentage of participants				
number (confidence interval 95%)	53.31 (47.00 to 59.62)	61.50 (55.31 to 67.70)		

Statistical analyses

Statistical analysis title	Pbo + Cobi + Vem vs Atezo + Cobi + Vem
Comparison groups	Arm A: Pbo + Cobi + Vem v Arm B: Atezo + Cobi + Vem
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0693
Method	Z-test
Parameter estimate	Difference in Event Free Rate
Point estimate	8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	17.04

Secondary: Time to Deterioration in Global Health Status (GHS) Determined Using

the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scale Score

End point title	Time to Deterioration in Global Health Status (GHS) Determined Using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Scale Score

End point description:

Time to deterioration in GHS/health-related quality of life (HRQoL)=time from randomization to first observed ≥10-point decrease in EORTC QLQ-C30 linearly transformed GHS/HRQoL scale score sustained for 2 consecutive assessments or followed by death while participant is on treatment. EORTC QLQ-C30 has 30 questions & assess 5 aspects of participant functioning (physical, emotional, role, cognitive &social), 3 symptom scales (fatigue, nausea, vomiting &pain), GHS/QoL & 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea &financial difficulties). GHS/QoL scored on a 7-point scale (1=Very Poor - 7=Excellent). Obtained scores are linearly transformed to score range of 0-100. Higher scores=higher response level & better QoL. ITT population. 9999=median & upper limit of 95% confidence interval (CI) was not estimable due to insufficient number of participants with event. 99999=upper limit of 95% CI was not estimable due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

Baseline up to PD or death due to any cause, whichever occurred first (up to approximately 33 months)

End point values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	256		
Units: months				
median (confidence interval 95%)	9999 (15.0 to 9999)	14.4 (9.2 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration in Physical Functioning (PF) Determined Using EORTC QLQ-C30 Scale Score

End point title	Time to Deterioration in Physical Functioning (PF) Determined Using EORTC QLQ-C30 Scale Score

End point description:

Time to deterioration in PF=time from randomization to first observed ≥10-point decrease in EORTC QLQ-C30 linearly transformed PF scale score sustained for 2 consecutive assessments or followed by death while participant is on treatment. EORTC QLQ-C30 has 30 questions & assess 5 aspects of participant functioning (physical, emotional, role, cognitive &social), 3 symptom scales (fatigue, nausea, vomiting &pain), GHS/QoL & 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea &financial difficulties). PF scale=5 questions about PF & daily activities (strenuous activities, long & short walks, bed/chair rest &needing help with eating, dressing, washing themselves/using the toilet). PF scored on 4-point scale (1=Not at All-4=Very Much). Obtained scores linearly transformed to score range of 0-100, higher scores=higher response level, functioning/support. ITT population. 9999= upper limit of 95% CI was not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Baseline up to PD or death due to any cause, whichever occurred first (up to approximately 33 months)

End point values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	256		
Units: months				
median (confidence interval 95%)	22.4 (15.7 to 9999)	17.5 (11.7 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

AE=any untoward medical occurrence in a participant when administered a pharmaceutical product regardless of causal relationship with this treatment. AE can therefore be any unfavorable & unintended sign, symptom/disease temporally associated with use of an investigational product, whether or not considered related to investigational product. SAE=any significant hazard, contraindication, side effect that is fatal or life-threatening, requires hospitalization/prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is medically significant or requires intervention to prevent one or other of outcomes listed above. All AEs were reported until 30 days & SAEs until 90 days after the final dose of study treatment or until initiation of subsequent anti-cancer therapy, whichever occurred first. Safety population included all participants who received any amount of any atezolizumab, cobimetinib, or vemurafenib.

End point type	Secondary

End point timeframe:

Up to approximately 85 months

End point values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	279	232		
Units: percentage of participants				
number (not applicable)				
AEs	99.6	100		
SAEs	43.0	50.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Atezolizumab

End point title	Serum Concentration of Atezolizumab[1]

End point description:

Pharmacokinetic (PK)-evaluable population included all participants who have received any dose of atezolizumab and for whom at least one evaluable PK sample was collected. n=number of participants with data available for analysis at the specified timepoint.

End point type	Secondary

End point timeframe:

Pre-infusion Day 1 of Cycles 1-4; 30 minutes post-infusion Day 1 of Cycles 1 and 4; at Atezolizumab discontinuation (up to approximately 33 months) (1 Cycle = 28 days)

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: This endpoint is reporting data only for concentration of atezolizumab (Atezo + Cobi + Vem arm). Hence only this arm has been included.

End point values	Arm B: Atezo + Cobi + Vem			
Subject group type	Reporting group			
Number of subjects analysed	223			
Units: micrograms per milliliters (ug/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1/30 Min Postdose (n=187)	281 (± 111)			
Cycle 2 Day 1/Predose (n=186)	102 (± 47.4)			
Cycle 3 Day 1/Predose (n=171)	149 (± 61.9)			
Cycle 4 Day 1/Predose (n=159)	181 (± 75.5)			
Cycle 4 Day 1/30 Min Postdose (n=144)	431 (± 158)			
Study Drugs Discontinuation Visit (n=101)	122 (± 97.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Cobimetinib Dose: 20/40 mg

End point title	Plasma Concentration of Cobimetinib Dose: 20/40 mg

End point description:

The Cobi PK-evaluable population included all participants who received any dose of cobimetinib 20/40 mg and for whom at least one evaluable PK sample was collected. n=number of participants with data available for analysis at the specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) and 3 to 6 hours post dose on Day 15 of Cycles 1 and 4 (1 Cycle = 28 days)

End point values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	208		
Units: mg				
arithmetic mean (standard deviation)				
Cycle 1 Day 15/Predose (n=32,29)	79.9 (± 72.2)	144 (± 101)		
Cycle 1 Day 15/3-6 Hr Postdose (n=32,26)	167 (± 116)	216 (± 145)		
Cycle 4 Day 15/Predose (n=43,49)	108 (± 97.5)	92.3 (± 79.5)		
Cycle 4 Day 15/3-6 Hr Postdose (n=45,47)	167 (± 126)	171 (± 140)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Cobimetinib Dose: 60 mg

End point title	Plasma Concentration of Cobimetinib Dose: 60 mg

End point description:

The Cobi PK-evaluable population included all participants who received any dose of Cobimetinib 60 mg and for whom at least one evaluable PK sample was collected. n=number of participants with data available for analysis at the specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) and 3 to 6 hours post dose on Day 15 of Cycles 1 and 4 (1 Cycle = 28 days)

End point values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	208		
Units: mg				
arithmetic mean (standard deviation)				
Cycle 1 Day 15/Predose (n=170,148)	169 (± 171)	216 (± 188)		
Cycle 1 Day 15/3-6 Hr Postdose (n=171,140)	278 (± 206)	375 (± 243)		
Cycle 4 Day 15/Predose (n=123,112)	150 (± 113)	151 (± 120)		
Cycle 4 Day 15/3-6 Hr Postdose (n=120,109)	240 (± 195)	256 (± 197)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Vemurafenib

End point title	Plasma Concentration of Vemurafenib

End point description:

The Vem PK-evaluable population included all participants who received any dose of vemurafenib and for whom at least one evaluable PK sample was collected. n=number of participants with data available for analysis at the specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) and 3 to 6 hours post dose on Day 15 of Cycles 1 and 4 (1 Cycle = 28 days)

End point values	Arm A: Pbo + Cobi + Vem	Arm B: Atezo + Cobi + Vem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	209		
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 15/ predose (n=199,179)	38.9 (± 100)	27.0 (± 102)		
Cycle 1 Day 15/ 3-6 hr (n=205,168)	41.3 (± 57.7)	28.0 (± 88.6)		
Cycle 4 Day 15/ predose (n=168,158)	39.2 (± 105)	24.7 (± 202)		
Cycle 4 Day 15/ 3-6 hr postdose (n=168,154)	42.3 (± 59.4)	26.5 (± 135)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Positive for Anti-drug Antibodies (ADA) to Atezolizumab

End point title	Percentage of Participants Positive for Anti-drug Antibodies (ADA) to Atezolizumab[2]

End point description:

Presence of ADAs against atezolizumab during the study relative to the presence of ADAs at baseline. The percentage of ADA-positive participants after drug administration were determined for participants exposed to atezolizumab. For determining post-baseline incidence, participants were considered to be ADA-positive if they were ADA-negative or had missing data at baseline but developed an ADA response following study drug exposure, or if they were ADA-positive at baseline and the titer of 1 or more post-baseline samples was at least 0.60 titer units (t.u.) greater than the baseline titer result. ADA-evaluable population included participants who received at least one dose of atezolizumab and had ≥ 1 post-baseline ADA result. n=number of participants with data available for analysis at the specified timepoint.

End point type	Secondary

End point timeframe:

Pre-infusion Day 1 of Cycles 1-4 (1 Cycle=28 days); at Atezolizumab discontinuation (approximately up to 33 months)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data only for ADA data for Atezolizumab, for the Atezo + Cobi + Vem arm. Hence only this arm has been included.

End point values	Arm B: Atezo + Cobi + Vem			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: percentage of participants				
number (not applicable)				
Baseline evaluable participants (n=208)	1.4			
Post−baseline evaluable participants (n=218)	13.3			

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Run-in Period: 28 days

Triple Combination Period: From the first dose of study treatment in the Triple Combination Period (Day 29) up to approximately 85 months

Adverse event reporting additional description:

Safety Population. 26 were included in the pbo+cobi+vem arm for safety (22 participants in atezo+cobi+vem arm stopped run-in treatment & 4 in atezo+cobi+vem arm completed the run-in treatment but none received atezo). 2 participants in pbo+cobi+vem arm received atezo & were considered in the atezo+cobi+vem arm for safety analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Run-in - Pbo + Cobi + Vem

Reporting group description:

Participants received vemurafenib, 960 mg (four, 240 mg tablets), PO, BID along with cobimetinib, 60 mg (three, 20 mg tablets) PO, QD on Days 1 to 21 only followed by vemurafenib 960 mg (four, 240 mg tablets), PO, BID on Days 22 to 28 during the 28 day run-in period.

Reporting group title	Triple combination: Pbo + Cobi + Vem

Reporting group description:

After the 28-day run-in, participants received atezolizumab matching placebo as IV infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21 and vemurafenib 960 mg (four, 240 mg tablets) PO, BID on Days 1 to 28. Study treatment was continued until investigator determined PD, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.

Reporting group title	Triple combination: Atezo + Cobi + Vem

Reporting group description:

After the 28-day run-in period, participants received atezolizumab 840 mg as IV infusion on Days 1 and 15, cobimetinib, 60 mg (three, 20 mg tablets) PO, QD, on Days 1 to 21, vemurafenib 720 mg (three, 240 mg tablets) PO BID on Days 1 to 28, and vemurafenib placebo (1 tablet) PO BID on Days 1 to 28. Study treatment was continued until investigator determined PD, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurred first.

Reporting group title	Run-in - Atezo + Cobi + Vem

Reporting group description:

Participants received vemurafenib, 960 mg (four, 240 mg tablets) PO, BID along with cobimetinib 60 mg (three, 20 mg tablets) PO, QD on Days 1 to 21 only followed by vemurafenib 720 mg (three, 240 mg tablets) PO, BID and vemurafenib matching placebo, PO, BID on Days 22 to 28 during the 28 day run-in period.

Serious adverse events	Run-in - Pbo + Cobi + Vem	Triple combination: Pbo + Cobi + Vem	Triple combination: Atezo + Cobi + Vem
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 279 (17.92%)	81 / 279 (29.03%)	109 / 232 (46.98%)
number of deaths (all causes)	25	149	128
number of deaths resulting from adverse events	0	1	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Malignant melanoma in situ			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip neoplasm			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Breast cancer			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Papillary thyroid cancer			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibroma			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Keratoacanthoma			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Non-Hodgkin's lymphoma			

subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Tumour pain			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Liposarcoma			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melanocytic naevus			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Lentigo maligna			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Malignant melanoma			
subjects affected / exposed	0 / 279 (0.00%)	2 / 279 (0.72%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Prostate cancer			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Meningioma			

subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 279 (0.36%)	2 / 279 (0.72%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 279 (0.36%)	3 / 279 (1.08%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	1 / 1	1 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Influenza like illness			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Fatigue			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Pyrexia			
subjects affected / exposed	7 / 279 (2.51%)	6 / 279 (2.15%)	13 / 232 (5.60%)
occurrences causally related to treatment / all	6 / 7	4 / 7	13 / 18
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian rupture			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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

Pelvic pain			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Prostatitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	3 / 232 (1.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 279 (0.00%)	3 / 279 (1.08%)	5 / 232 (2.16%)
occurrences causally related to treatment / all	0 / 0	0 / 3	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Lung disorder			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pleural effusion			
subjects affected / exposed	0 / 279 (0.00%)	2 / 279 (0.72%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord leukoplakia			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol abuse			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Mental status changes			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Confusional state			

subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	0 / 232 (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
Lipase increased			
subjects affected / exposed	1 / 279 (0.36%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	0 / 232 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 279 (0.00%)	2 / 279 (0.72%)	4 / 232 (1.72%)
occurrences causally related to treatment / all	0 / 0	2 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			

subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 279 (1.79%)	2 / 279 (0.72%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	5 / 6	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 279 (0.00%)	2 / 279 (0.72%)	5 / 232 (2.16%)
occurrences causally related to treatment / all	0 / 0	2 / 2	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Sternal fracture			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face injury			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			

subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 279 (0.00%)	2 / 279 (0.72%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	3 / 232 (1.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericarditis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Arrhythmia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure			

subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	3 / 232 (1.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	1 / 279 (0.36%)	1 / 279 (0.36%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Coronary artery occlusion			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			

subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Palpitations			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 279 (0.00%)	2 / 279 (0.72%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre syndrome			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Epilepsy			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	4 / 232 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertonia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Transient ischaemic attack			

subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Haemorrhagic stroke			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis autoimmune			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated encephalitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Syncope			

subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	3 / 232 (1.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Cerebrovascular accident			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Seizure			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bell's palsy			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain dislocation syndrome			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			

subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Leukopenia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agranulocytosis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 279 (0.00%)	2 / 279 (0.72%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal artery embolism			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Central serous chorioretinopathy			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	0 / 232 (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
Eye pain			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			

subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Maculopathy			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Detachment of retinal pigment epithelium			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	0 / 232 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Pancreatitis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intussusception			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Faecaloma			

subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	0 / 232 (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 ulcer			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Gastritis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Obstructive pancreatitis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Vomiting			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis haemorrhagic			

subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Abdominal pain			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Diarrhoea			
subjects affected / exposed	1 / 279 (0.36%)	3 / 279 (1.08%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	1 / 1	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis necrotising			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Autoimmune pancreatitis			

subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	4 / 232 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune hepatitis			
subjects affected / exposed	0 / 279 (0.00%)	3 / 279 (1.08%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hepatitis fulminant			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Cholecystitis acute			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	3 / 232 (1.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune cholangitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 279 (1.79%)	0 / 279 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Rash erythematous			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Neutrophilic dermatosis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Purpura			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Angioedema			

subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Photosensitivity reaction			
subjects affected / exposed	0 / 279 (0.00%)	2 / 279 (0.72%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema multiforme			
subjects affected / exposed	2 / 279 (0.72%)	0 / 279 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash papular			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	4 / 279 (1.43%)	0 / 279 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic skin eruption			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	2 / 279 (0.72%)	0 / 279 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			

subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	6 / 232 (2.59%)
occurrences causally related to treatment / all	1 / 1	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Renal failure			
subjects affected / exposed	1 / 279 (0.36%)	1 / 279 (0.36%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Prerenal failure			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 279 (0.00%)	2 / 279 (0.72%)	3 / 232 (1.29%)
occurrences causally related to treatment / all	0 / 0	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fracture pain			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Arthralgia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercreatinaemia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			

subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Erysipelas			
subjects affected / exposed	2 / 279 (0.72%)	2 / 279 (0.72%)	4 / 232 (1.72%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Pneumonia			
subjects affected / exposed	2 / 279 (0.72%)	3 / 279 (1.08%)	8 / 232 (3.45%)
occurrences causally related to treatment / all	0 / 2	2 / 3	4 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Upper respiratory tract infection			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 279 (0.00%)	2 / 279 (0.72%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial prostatitis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Serratia bacteraemia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
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	0 / 279 (0.00%)	2 / 279 (0.72%)	3 / 232 (1.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			

subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Bartholin's abscess			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal abscess			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Encephalitis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			

subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Appendicitis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Bacteraemia			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	0 / 232 (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
Meningitis aseptic			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine infection			
subjects affected / exposed	0 / 279 (0.00%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bacterial infection			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			

subjects affected / exposed	2 / 279 (0.72%)	0 / 279 (0.00%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Atypical pneumonia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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
Hyperglycaemia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 279 (0.36%)	1 / 279 (0.36%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 279 (0.00%)	0 / 279 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 279 (0.00%)	2 / 279 (0.72%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 279 (0.00%)	0 / 232 (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

Serious adverse events	Run-in - Atezo + Cobi + Vem		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 232 (9.05%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lip neoplasm				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Papillary thyroid cancer				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fibroma				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Keratoacanthoma				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-Hodgkin's lymphoma				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liposarcoma				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melanocytic naevus				

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lentigo maligna				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningioma				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertension				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Shock haemorrhagic				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
General physical health deterioration				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Systemic inflammatory response syndrome				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza like illness				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 232 (0.86%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				

Sarcoidosis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian rupture			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pelvic pain			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostatitis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary haemorrhage				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				

subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute pulmonary oedema			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vocal cord leukoplakia			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alcohol abuse			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			

subjects affected / exposed	1 / 232 (0.43%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	1 / 232 (0.43%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ejection fraction decreased				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
White blood cell count decreased				
subjects affected / exposed	1 / 232 (0.43%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	1 / 232 (0.43%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood creatine phosphokinase increased				
subjects affected / exposed	1 / 232 (0.43%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Alanine aminotransferase increased				

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QT prolonged				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Sternal fracture				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Face injury				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infusion related reaction				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Myocardial infarction				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 232 (0.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular arrhythmia				

subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Left ventricular failure			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stress cardiomyopathy			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery occlusion			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Palpitations			

subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Guillain-Barre syndrome			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hydrocephalus			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertonia			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic stroke			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalitis autoimmune			

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune-mediated encephalitis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aphasia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lethargy				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral sensorimotor neuropathy				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bell's palsy				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Brain dislocation syndrome				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Thrombocytopenia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Agranulocytosis				

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Retinal artery embolism				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Central serous chorioretinopathy				
subjects affected / exposed	1 / 232 (0.43%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye pain				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uveitis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Maculopathy				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Detachment of retinal pigment				

epithelium			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Volvulus			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intussusception			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Faecaloma			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis erosive			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstructive pancreatitis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis haemorrhagic				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Autoimmune colitis				

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 232 (0.43%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis necrotising				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Autoimmune pancreatitis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hypertransaminasaemia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis				

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Autoimmune hepatitis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis fulminant				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatotoxicity				
subjects affected / exposed	1 / 232 (0.43%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Autoimmune cholangitis				

subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash erythematous			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutrophilic dermatosis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Purpura			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angioedema			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Photosensitivity reaction			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erythema multiforme			

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash papular				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				
subjects affected / exposed	2 / 232 (0.86%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Toxic skin eruption				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug reaction with eosinophilia and systemic symptoms				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Nephritis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute kidney injury				
subjects affected / exposed	1 / 232 (0.43%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				

subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prerenal failure			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypophysitis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fracture pain			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Arthralgia			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myositis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercreatinaemia			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rhabdomyolysis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Erysipelas			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pharyngotonsillitis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial prostatitis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Serratia bacteraemia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 232 (0.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bartholin's abscess				

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Localised infection				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 232 (0.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal abscess				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalitis				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oral herpes				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis aseptic				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine infection				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial infection				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyponatraemia				
subjects affected / exposed	2 / 232 (0.86%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Type 2 diabetes mellitus				
subjects affected / exposed	0 / 232 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				

subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Run-in - Pbo + Cobi + Vem	Triple combination: Pbo + Cobi + Vem	Triple combination: Atezo + Cobi + Vem
Total subjects affected by non-serious adverse events			
subjects affected / exposed	262 / 279 (93.91%)	222 / 279 (79.57%)	226 / 232 (97.41%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 279 (0.36%)	15 / 279 (5.38%)	7 / 232 (3.02%)
occurrences (all)	1	22	9
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 279 (7.53%)	39 / 279 (13.98%)	36 / 232 (15.52%)
occurrences (all)	21	52	45
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 279 (6.81%)	36 / 279 (12.90%)	50 / 232 (21.55%)
occurrences (all)	22	68	101
Chills			
subjects affected / exposed	13 / 279 (4.66%)	11 / 279 (3.94%)	18 / 232 (7.76%)
occurrences (all)	13	19	20
Pain			
subjects affected / exposed	1 / 279 (0.36%)	8 / 279 (2.87%)	13 / 232 (5.60%)
occurrences (all)	1	8	14
Mucosal inflammation			
subjects affected / exposed	5 / 279 (1.79%)	12 / 279 (4.30%)	12 / 232 (5.17%)
occurrences (all)	5	16	25
Pyrexia			

subjects affected / exposed	48 / 279 (17.20%)	58 / 279 (20.79%)	93 / 232 (40.09%)
occurrences (all)	54	120	203
Fatigue			
subjects affected / exposed	38 / 279 (13.62%)	56 / 279 (20.07%)	50 / 232 (21.55%)
occurrences (all)	41	84	74
Influenza like illness			
subjects affected / exposed	4 / 279 (1.43%)	12 / 279 (4.30%)	19 / 232 (8.19%)
occurrences (all)	4	14	24
Oedema peripheral			
subjects affected / exposed	13 / 279 (4.66%)	27 / 279 (9.68%)	45 / 232 (19.40%)
occurrences (all)	14	36	59
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 279 (1.43%)	18 / 279 (6.45%)	18 / 232 (7.76%)
occurrences (all)	4	19	28
Pneumonitis			
subjects affected / exposed	0 / 279 (0.00%)	13 / 279 (4.66%)	29 / 232 (12.50%)
occurrences (all)	0	18	36
Oropharyngeal pain			
subjects affected / exposed	4 / 279 (1.43%)	10 / 279 (3.58%)	24 / 232 (10.34%)
occurrences (all)	5	12	26
Cough			
subjects affected / exposed	8 / 279 (2.87%)	26 / 279 (9.32%)	35 / 232 (15.09%)
occurrences (all)	8	32	63
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 279 (1.79%)	17 / 279 (6.09%)	13 / 232 (5.60%)
occurrences (all)	5	19	17
Investigations			
Ejection fraction decreased			
subjects affected / exposed	2 / 279 (0.72%)	6 / 279 (2.15%)	13 / 232 (5.60%)
occurrences (all)	2	6	14
Blood alkaline phosphatase increased			
subjects affected / exposed	19 / 279 (6.81%)	33 / 279 (11.83%)	33 / 232 (14.22%)
occurrences (all)	20	46	70
Gamma-glutamyltransferase increased			

subjects affected / exposed	5 / 279 (1.79%)	16 / 279 (5.73%)	15 / 232 (6.47%)
occurrences (all)	5	21	20
Aspartate aminotransferase increased			
subjects affected / exposed	20 / 279 (7.17%)	42 / 279 (15.05%)	66 / 232 (28.45%)
occurrences (all)	22	61	133
Amylase increased			
subjects affected / exposed	17 / 279 (6.09%)	40 / 279 (14.34%)	46 / 232 (19.83%)
occurrences (all)	20	72	91
Blood creatinine increased			
subjects affected / exposed	17 / 279 (6.09%)	35 / 279 (12.54%)	42 / 232 (18.10%)
occurrences (all)	17	62	119
Blood creatine phosphokinase increased			
subjects affected / exposed	67 / 279 (24.01%)	96 / 279 (34.41%)	108 / 232 (46.55%)
occurrences (all)	74	308	328
Blood lactate dehydrogenase increased			
subjects affected / exposed	5 / 279 (1.79%)	9 / 279 (3.23%)	19 / 232 (8.19%)
occurrences (all)	5	15	32
Blood bilirubin increased			
subjects affected / exposed	8 / 279 (2.87%)	11 / 279 (3.94%)	24 / 232 (10.34%)
occurrences (all)	8	18	75
Lipase increased			
subjects affected / exposed	20 / 279 (7.17%)	75 / 279 (26.88%)	77 / 232 (33.19%)
occurrences (all)	27	200	184
Weight decreased			
subjects affected / exposed	7 / 279 (2.51%)	8 / 279 (2.87%)	13 / 232 (5.60%)
occurrences (all)	7	12	13
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 279 (0.00%)	11 / 279 (3.94%)	13 / 232 (5.60%)
occurrences (all)	0	12	16
Alanine aminotransferase increased			
subjects affected / exposed	24 / 279 (8.60%)	52 / 279 (18.64%)	73 / 232 (31.47%)
occurrences (all)	25	69	127
Injury, poisoning and procedural complications			

Sunburn			
subjects affected / exposed	10 / 279 (3.58%)	26 / 279 (9.32%)	21 / 232 (9.05%)
occurrences (all)	10	50	47
Infusion related reaction			
subjects affected / exposed	0 / 279 (0.00%)	18 / 279 (6.45%)	24 / 232 (10.34%)
occurrences (all)	0	24	31
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 279 (1.43%)	12 / 279 (4.30%)	15 / 232 (6.47%)
occurrences (all)	4	13	16
Headache			
subjects affected / exposed	16 / 279 (5.73%)	45 / 279 (16.13%)	55 / 232 (23.71%)
occurrences (all)	16	71	95
Dysgeusia			
subjects affected / exposed	5 / 279 (1.79%)	6 / 279 (2.15%)	15 / 232 (6.47%)
occurrences (all)	5	6	17
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	3 / 279 (1.08%)	13 / 279 (4.66%)	17 / 232 (7.33%)
occurrences (all)	3	19	47
Anaemia			
subjects affected / exposed	9 / 279 (3.23%)	37 / 279 (13.26%)	44 / 232 (18.97%)
occurrences (all)	11	62	78
Eye disorders			
Vision blurred			
subjects affected / exposed	8 / 279 (2.87%)	12 / 279 (4.30%)	12 / 232 (5.17%)
occurrences (all)	9	17	15
Central serous chorioretinopathy			
subjects affected / exposed	19 / 279 (6.81%)	27 / 279 (9.68%)	25 / 232 (10.78%)
occurrences (all)	19	34	33
Dry eye			
subjects affected / exposed	2 / 279 (0.72%)	2 / 279 (0.72%)	14 / 232 (6.03%)
occurrences (all)	2	2	15
Uveitis			
subjects affected / exposed	0 / 279 (0.00%)	12 / 279 (4.30%)	13 / 232 (5.60%)
occurrences (all)	0	14	18
Gastrointestinal disorders			

Stomatitis			
subjects affected / exposed	6 / 279 (2.15%)	11 / 279 (3.94%)	15 / 232 (6.47%)
occurrences (all)	6	15	30
Dyspepsia			
subjects affected / exposed	5 / 279 (1.79%)	16 / 279 (5.73%)	14 / 232 (6.03%)
occurrences (all)	5	23	17
Abdominal pain upper			
subjects affected / exposed	11 / 279 (3.94%)	21 / 279 (7.53%)	20 / 232 (8.62%)
occurrences (all)	11	29	23
Vomiting			
subjects affected / exposed	31 / 279 (11.11%)	45 / 279 (16.13%)	45 / 232 (19.40%)
occurrences (all)	31	72	63
Dry mouth			
subjects affected / exposed	2 / 279 (0.72%)	10 / 279 (3.58%)	16 / 232 (6.90%)
occurrences (all)	2	10	17
Abdominal pain			
subjects affected / exposed	9 / 279 (3.23%)	22 / 279 (7.89%)	28 / 232 (12.07%)
occurrences (all)	11	39	44
Diarrhoea			
subjects affected / exposed	113 / 279 (40.50%)	85 / 279 (30.47%)	74 / 232 (31.90%)
occurrences (all)	131	186	196
Nausea			
subjects affected / exposed	41 / 279 (14.70%)	64 / 279 (22.94%)	55 / 232 (23.71%)
occurrences (all)	41	96	97
Constipation			
subjects affected / exposed	21 / 279 (7.53%)	16 / 279 (5.73%)	30 / 232 (12.93%)
occurrences (all)	21	24	36
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	2 / 279 (0.72%)	14 / 279 (5.02%)	4 / 232 (1.72%)
occurrences (all)	3	22	8
Rash			
subjects affected / exposed	81 / 279 (29.03%)	63 / 279 (22.58%)	71 / 232 (30.60%)
occurrences (all)	96	106	121
Alopecia			

subjects affected / exposed	2 / 279 (0.72%)	25 / 279 (8.96%)	24 / 232 (10.34%)
occurrences (all)	2	27	24
Photosensitivity reaction			
subjects affected / exposed	40 / 279 (14.34%)	45 / 279 (16.13%)	40 / 232 (17.24%)
occurrences (all)	42	66	63
Dermatitis acneiform			
subjects affected / exposed	28 / 279 (10.04%)	23 / 279 (8.24%)	29 / 232 (12.50%)
occurrences (all)	28	34	43
Hyperkeratosis			
subjects affected / exposed	2 / 279 (0.72%)	8 / 279 (2.87%)	12 / 232 (5.17%)
occurrences (all)	2	13	13
Dry skin			
subjects affected / exposed	7 / 279 (2.51%)	21 / 279 (7.53%)	28 / 232 (12.07%)
occurrences (all)	7	24	30
Pruritus			
subjects affected / exposed	18 / 279 (6.45%)	34 / 279 (12.19%)	53 / 232 (22.84%)
occurrences (all)	19	66	104
Erythema			
subjects affected / exposed	15 / 279 (5.38%)	33 / 279 (11.83%)	36 / 232 (15.52%)
occurrences (all)	17	51	42
Rash maculo-papular			
subjects affected / exposed	44 / 279 (15.77%)	10 / 279 (3.58%)	19 / 232 (8.19%)
occurrences (all)	51	11	28
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 279 (0.36%)	28 / 279 (10.04%)	48 / 232 (20.69%)
occurrences (all)	1	31	62
Hypothyroidism			
subjects affected / exposed	3 / 279 (1.08%)	23 / 279 (8.24%)	46 / 232 (19.83%)
occurrences (all)	3	24	67
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 279 (0.72%)	18 / 279 (6.45%)	26 / 232 (11.21%)
occurrences (all)	2	20	32
Pain in extremity			

subjects affected / exposed	8 / 279 (2.87%)	25 / 279 (8.96%)	29 / 232 (12.50%)
occurrences (all)	8	38	51
Arthralgia			
subjects affected / exposed	42 / 279 (15.05%)	70 / 279 (25.09%)	84 / 232 (36.21%)
occurrences (all)	48	134	193
Muscle spasms			
subjects affected / exposed	1 / 279 (0.36%)	8 / 279 (2.87%)	14 / 232 (6.03%)
occurrences (all)	1	9	18
Myalgia			
subjects affected / exposed	12 / 279 (4.30%)	42 / 279 (15.05%)	52 / 232 (22.41%)
occurrences (all)	14	62	80
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 279 (1.43%)	22 / 279 (7.89%)	23 / 232 (9.91%)
occurrences (all)	4	23	28
Urinary tract infection			
subjects affected / exposed	3 / 279 (1.08%)	10 / 279 (3.58%)	21 / 232 (9.05%)
occurrences (all)	3	17	45
COVID-19			
subjects affected / exposed	0 / 279 (0.00%)	5 / 279 (1.79%)	13 / 232 (5.60%)
occurrences (all)	0	7	16
Influenza			
subjects affected / exposed	1 / 279 (0.36%)	10 / 279 (3.58%)	18 / 232 (7.76%)
occurrences (all)	1	13	27
Folliculitis			
subjects affected / exposed	0 / 279 (0.00%)	12 / 279 (4.30%)	12 / 232 (5.17%)
occurrences (all)	0	19	13
Conjunctivitis			
subjects affected / exposed	3 / 279 (1.08%)	13 / 279 (4.66%)	19 / 232 (8.19%)
occurrences (all)	3	14	21
Nasopharyngitis			
subjects affected / exposed	3 / 279 (1.08%)	27 / 279 (9.68%)	21 / 232 (9.05%)
occurrences (all)	3	41	41
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	7 / 279 (2.51%)	11 / 279 (3.94%)	18 / 232 (7.76%)
occurrences (all)	7	23	37
Hypokalaemia			
subjects affected / exposed	4 / 279 (1.43%)	12 / 279 (4.30%)	12 / 232 (5.17%)
occurrences (all)	5	17	14
Decreased appetite			
subjects affected / exposed	19 / 279 (6.81%)	25 / 279 (8.96%)	25 / 232 (10.78%)
occurrences (all)	20	38	29
Hypophosphataemia			
subjects affected / exposed	3 / 279 (1.08%)	15 / 279 (5.38%)	14 / 232 (6.03%)
occurrences (all)	3	27	49

Non-serious adverse events	Run-in - Atezo + Cobi + Vem		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	208 / 232 (89.66%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 232 (0.86%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 232 (4.74%)		
occurrences (all)	11		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 232 (4.74%)		
occurrences (all)	12		
Chills			
subjects affected / exposed	8 / 232 (3.45%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	7 / 232 (3.02%)		
occurrences (all)	7		

Pyrexia			
subjects affected / exposed	46 / 232 (19.83%)		
occurrences (all)	55		
Fatigue			
subjects affected / exposed	34 / 232 (14.66%)		
occurrences (all)	35		
Influenza like illness			
subjects affected / exposed	2 / 232 (0.86%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	9 / 232 (3.88%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 232 (1.29%)		
occurrences (all)	3		
Pneumonitis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	5 / 232 (2.16%)		
occurrences (all)	6		
Cough			
subjects affected / exposed	2 / 232 (0.86%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 232 (1.72%)		
occurrences (all)	4		
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	13 / 232 (5.60%)		
occurrences (all)	15		

Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 232 (0.86%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 232 (6.03%)		
occurrences (all)	14		
Amylase increased			
subjects affected / exposed	9 / 232 (3.88%)		
occurrences (all)	9		
Blood creatinine increased			
subjects affected / exposed	17 / 232 (7.33%)		
occurrences (all)	17		
Blood creatine phosphokinase increased			
subjects affected / exposed	48 / 232 (20.69%)		
occurrences (all)	52		
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 232 (1.72%)		
occurrences (all)	4		
Blood bilirubin increased			
subjects affected / exposed	6 / 232 (2.59%)		
occurrences (all)	6		
Lipase increased			
subjects affected / exposed	21 / 232 (9.05%)		
occurrences (all)	25		
Weight decreased			
subjects affected / exposed	2 / 232 (0.86%)		
occurrences (all)	2		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	14 / 232 (6.03%)		
occurrences (all)	14		
Injury, poisoning and procedural			

complications			
Sunburn			
subjects affected / exposed	12 / 232 (5.17%)		
occurrences (all)	14		
Infusion related reaction			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 232 (1.72%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	11 / 232 (4.74%)		
occurrences (all)	11		
Dysgeusia			
subjects affected / exposed	7 / 232 (3.02%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	3 / 232 (1.29%)		
occurrences (all)	3		
Anaemia			
subjects affected / exposed	3 / 232 (1.29%)		
occurrences (all)	3		
Eye disorders			
Vision blurred			
subjects affected / exposed	3 / 232 (1.29%)		
occurrences (all)	3		
Central serous chorioretinopathy			
subjects affected / exposed	9 / 232 (3.88%)		
occurrences (all)	9		
Dry eye			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences (all)	0		
Uveitis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences (all)	0		

Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	12 / 232 (5.17%)		
occurrences (all)	15		
Dyspepsia			
subjects affected / exposed	8 / 232 (3.45%)		
occurrences (all)	8		
Abdominal pain upper			
subjects affected / exposed	5 / 232 (2.16%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	16 / 232 (6.90%)		
occurrences (all)	18		
Dry mouth			
subjects affected / exposed	3 / 232 (1.29%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	4 / 232 (1.72%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	78 / 232 (33.62%)		
occurrences (all)	90		
Nausea			
subjects affected / exposed	37 / 232 (15.95%)		
occurrences (all)	38		
Constipation			
subjects affected / exposed	9 / 232 (3.88%)		
occurrences (all)	10		
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	62 / 232 (26.72%)		
occurrences (all)	67		
Alopecia			

subjects affected / exposed	1 / 232 (0.43%)		
occurrences (all)	1		
Photosensitivity reaction			
subjects affected / exposed	16 / 232 (6.90%)		
occurrences (all)	16		
Dermatitis acneiform			
subjects affected / exposed	12 / 232 (5.17%)		
occurrences (all)	13		
Hyperkeratosis			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	6 / 232 (2.59%)		
occurrences (all)	6		
Pruritus			
subjects affected / exposed	24 / 232 (10.34%)		
occurrences (all)	28		
Erythema			
subjects affected / exposed	10 / 232 (4.31%)		
occurrences (all)	10		
Rash maculo-papular			
subjects affected / exposed	31 / 232 (13.36%)		
occurrences (all)	34		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences (all)	1		
Hypothyroidism			
subjects affected / exposed	2 / 232 (0.86%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 232 (0.86%)		
occurrences (all)	2		
Pain in extremity			

subjects affected / exposed	8 / 232 (3.45%)		
occurrences (all)	9		
Arthralgia			
subjects affected / exposed	33 / 232 (14.22%)		
occurrences (all)	34		
Muscle spasms			
subjects affected / exposed	2 / 232 (0.86%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	17 / 232 (7.33%)		
occurrences (all)	18		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 232 (1.29%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences (all)	1		
COVID-19			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	2 / 232 (0.86%)		
occurrences (all)	2		
Folliculitis			
subjects affected / exposed	1 / 232 (0.43%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	0 / 232 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	4 / 232 (1.72%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	4 / 232 (1.72%)		
occurrences (all)	4		
Hypokalaemia			
subjects affected / exposed	6 / 232 (2.59%)		
occurrences (all)	6		
Decreased appetite			
subjects affected / exposed	12 / 232 (5.17%)		
occurrences (all)	12		
Hypophosphataemia			
subjects affected / exposed	5 / 232 (2.16%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2017	The following changes were made as per amendment 3: Inclusion criteria were added to include participants with prior neoadjuvant and adjuvant chemotherapy. Additional laboratory tests were added for safety. Inclusion criteria for BRAF testing and measurable disease were clarified. Exclusion criteria language for cancer-related, ocular, cardiac, and central nervous system was updated for clarification. Language for history of autoimmune disease in Additional Exclusion Criteria was updated for clarification and Appendix 9 was added. Exclusion criteria for Grade >= 3 hemorrhage or bleeding, history of stroke, reversible ischemic neurological defect and transient ischemic attack were added to the Additional Exclusion Criteria for clarification; The dosing window for vemurafenib was amended to ensure dosing is not exceeded if a dose is missed; Tumor and response evaluations were clarified; Language for participant reported outcomes was updated for clarification; participant discontinuation was updated to include participants who develop a contraindication to atezolizumab for clarification. Study treatment discontinuation was updated to include cases of discontinuation of one or two study drugs for clarification; Risks associated with vemurafenib were updated including the addition of Dupuytren's contracture and plantar fascial fibromatosis and updating RVO and QTc interval; Management of participants who experience specific AEs was reformatted for clarity to include sections for dose modifications during the run-in period and for dose modifications during the triplet-treatment period.;The re porting of the term "sudden death" was updated to also require the presumed cause of death; Language for secondary and exploratory efficacy endpoints was updated for clarification.
05 March 2018	The following changes were made as per amendment 4: It was clarified that response was to assessed by investigator until disease progression or death, whichever occurred first; Evaluation of tumor response conforming to RECIST v1.1 through 24 months was clarified to occur, for example, on Weeks 8, 16, 24, 32, etc., not the last week of Cycles 1, 3, 5, 7, etc; Dose modification of vemurafenib during the triplet treatment period was added; It was clarified that pre-dose PK samples should always be drawn on Day 1 of Cycles 1-4 and Day 15 of Cycles 1 and 4.
30 October 2018	The following changes were made as per amendment 5: The inclusion criterion that addresses female contraception was modified to specify when women must refrain from donating eggs; Lists of risks for atezolizumab and guidelines for managing participants who experience atezolizumab-associated AEs were revised to include nephritis; The maximum time for interrupting atezolizumab treatment was changed from 105 days to 12 weeks for consistency with the guidelines for management of atezolizumab-associated AEs. It was clarified that if vemurafenib is discontinued and study treatment (cobimetinib and or atezolizumab/atezolizumab placebo) continues, ECGs are required as per standard of care or as clinically indicated (Appendix 1); Appendix 2 was amended to indicate that biomarker plasma samples are no longer required after atezolizumab is discontinued.

12 February 2020	The following changes were made as per amendment 6: The list of atezolizumab risks was updated to include myositis for consistency with the list of identified risks in the Atezolizumab Investigator's Brochure; To address a request by the French National Agency for the Safety of Medicines and Health Products (ANSM), systemic immune activation was replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab (Section 5.1.1) and the management guidelines for systemic immune activation have been replaced with management guidelines for hemophagocytic lymphohistiocytosis and macrophage activation syndrome. In addition, systemic immune activation was removed from the list of adverse events of special interest; Language was updated to indicate that therapeutic or elective abortions were not considered adverse events unless performed because of an underlying maternal or embryofetal toxicity. In such cases, the underlying toxicity should be reported as a SAE; If atezolizumab/atezolizumab placebo treatment was interrupted or discontinued, ECGs was performed at the Day 1 visit of the following cycle to facilitate procedures for participants.
03 March 2021	The following changes were made as per amendment 7: The list of approved indications for atezolizumab was updated to include hepatocellular carcinoma and melanoma; Lists of identified risks for atezolizumab was revised to include severe cutaneous adverse reactions.
28 February 2022	The following changes were made as per amendment 8: The responsibilities of the investigator and the role of the Medical Monitor in breaking the treatment code (Section 4.2 of Protocol v8), determining participant eligibility and decision-making with respect to re-challenging participants with atezolizumab following treatment interruption have been clarified; The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, v18.
16 March 2023	The changes made as per amendment 9: General guidelines regarding Post-Trial Access to Cobimetinib, Vemurafenib, and Atezolizumab were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported