Clinical trial results:
A Phase II Two Cohort Study Evaluating the Safety and Efficacy of Cobimetinib plus Atezolizumab in BRAFV600 Wild-type melanoma with central nervous system metastases and cobimetinib plus atezolizumab and vemurafenib in BRAFV600 mutation-positive melanoma with central nervous system metastases

Summary

EudraCT number	2018-000759-41
Trial protocol	LV HU ES DE IT
Global end of trial date	13 April 2023

Results information

Result version number	v3 (current)
This version publication date	21 April 2024
First version publication date	21 July 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MO39136

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03625141
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to evaluate the efficacy and safety of cobimetinib plus atezolizumab in participants with BRAFV600 wild-type melanoma with central nervous system (CNS) metastases and of cobimetinib plus atezolizumab and vemurafenib in BRAFV600 mutation-positive melanoma patients with CNS metastases.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 December 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 18
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Switzerland: 5
Worldwide total number of subjects	80
EEA total number of subjects	57

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)	56
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 21 centers in 7 countries.

Pre-assignment

Screening details:

A total of 80 participants were enrolled at 21 centers.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1- cobimetinib and atezolizumab

Arm description:

Participants with BRAFV600 wild-type disease will be administered cobimetinib on Days 1−21 of each 28-day cycle; and atezolizumab on Days 1 and 15 of each treatment cycle.

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

Dosage and administration details:

Atezolizumab was given at a fixed dose of 840 mg by intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle

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

Dosage and administration details:

60 mg (three tablets of 20 mg each) orally (PO) once a day (QD) on Days 1−21 of each 28-day cycle.

Arm title	Cohort 2 - cobimetinib, atezolizumab and vemurafenib

Arm description:

Participants with BRAFV600 mutation-positive disease will be administered cobimetinib, atezolizumab and vemurafenib in 28-day treatment cycles. Treatment includes a 28-day run-in period where participants will receive cobimetinib and vemurafenib only. Upon completion of the 28-day run-in period, atezolizumab will be added to their treatment regimen

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

Dosage and administration details:

60 mg (three tablets of 20 mg each) PO QD on Days 1−21 of each 28-day cycle.

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

Dosage and administration details:

Participants received vemurafenib 960 mg (four 240 mg tablets) PO twice daily (BID) on days 1-21 of the run-in period (cycle 1); thereafter, they received vemurafenib 720 mg dose (three 240 mg tablets) PO BID on days 22-28 of cycle 1 and on days 1-28 of all subsequent cycles.

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

Dosage and administration details:

Atezolizumab was given at a fixed dose of 840 mg by IV infusion on Days 1 and 15 of each 28-day cycle. Only for cohort 2, no dose of atezolizumab was given during the run-in period (cycle 1).

Number of subjects in period 1	Cohort 1- cobimetinib and atezolizumab	Cohort 2 - cobimetinib, atezolizumab and vemurafenib
Started	15	65
Completed	0	0
Not completed	15	65
Consent withdrawn by subject	3	-
Adverse Event	-	2
Death	11	47
Study terminated by sponsor	1	13
Withdrawal of consent	-	1
Progressive disease	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1- cobimetinib and atezolizumab
Reporting group description:	
Participants with BRAFV600 wild-type disease will be administered cobimetinib on Days 1−21 of each 28-day cycle; and atezolizumab on Days 1 and 15 of each treatment cycle.	
Reporting group title	Cohort 2 - cobimetinib, atezolizumab and vemurafenib
Reporting group description:	
Participants with BRAFV600 mutation-positive disease will be administered cobimetinib, atezolizumab and vemurafenib in 28-day treatment cycles. Treatment includes a 28-day run-in period where participants will receive cobimetinib and vemurafenib only. Upon completion of the 28-day run-in period, atezolizumab will be added to their treatment regimen	

Reporting group values	Cohort 1- cobimetinib and atezolizumab	Cohort 2 - cobimetinib, atezolizumab and vemurafenib	Total
Number of subjects	15	65	80
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	48	56
From 65-84 years	7	17	24
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	60.9	54.4	
standard deviation	± 12.5	± 13.9	-
Gender Categorical Units: Subjects			
Female	9	24	33
Male	6	41	47
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	9	9
Not Hispanic or Latino	11	50	61
Not Stated	0	5	5
Unknown	4	1	5
Race (NIH/OMB) Units: Subjects			
White	11	61	72
Unknown	4	4	8

End points

End points reporting groups

Reporting group title	Cohort 1- cobimetinib and atezolizumab
Reporting group description:	
Participants with BRAFV600 wild-type disease will be administered cobimetinib on Days 1−21 of each 28-day cycle; and atezolizumab on Days 1 and 15 of each treatment cycle.	
Reporting group title	Cohort 2 - cobimetinib, atezolizumab and vemurafenib
Reporting group description:	
Participants with BRAFV600 mutation-positive disease will be administered cobimetinib, atezolizumab and vemurafenib in 28-day treatment cycles. Treatment includes a 28-day run-in period where participants will receive cobimetinib and vemurafenib only. Upon completion of the 28-day run-in period, atezolizumab will be added to their treatment regimen	
Subject analysis set title	PRO-evaluable Population: Cohort 1
Subject analysis set type	Per protocol
Subject analysis set description:	
All participants who received any amount of any study medication (e.g., atezolizumab, cobimetinib, or vemurafenib) and had a baseline and at least one post baseline PRO assessment in the questionnaire of interest (EORTC QLQ-C30 or EORTC QLQBN20)	
Subject analysis set title	PRO-evaluable Population: Cohort 2
Subject analysis set type	Per protocol
Subject analysis set description:	
All participants who received any amount of any study medication (e.g., atezolizumab, cobimetinib, or vemurafenib) and had a baseline and at least one post baseline PRO assessment in the questionnaire of interest (EORTC QLQ-C30 or EORTC QLQBN20)	
Subject analysis set title	Safety-evaluable Population: Cohort 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all participants who received at least one dose of study treatment.	
Subject analysis set title	Safety-evaluable Population: Cohort 2
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all participants who received at least one dose of study treatment.	
Subject analysis set title	Safety-evaluable Population: Cohort 2 (no atezolizumab)
Subject analysis set type	Safety analysis
Subject analysis set description:	
There were 5 participants in Cohort 2 administered with cobimetinib and vemurafenib only as they dropped out during the run-in period.	
Subject analysis set title	Evaluable Population: Cohort 1
Subject analysis set type	Per protocol
Subject analysis set description:	
The evaluable population included all enrolled participants who received study medication and had at least two post-baseline intracranial tumour assessments for response evaluation.	
Subject analysis set title	Evaluable Population: Cohort 2
Subject analysis set type	Per protocol
Subject analysis set description:	
The evaluable population included all enrolled participants who received study medication and had at least two post-baseline intracranial tumour assessments for response evaluation.	

Primary: Intracranial Objective Response Rate (ORR)

End point title	Intracranial Objective Response Rate (ORR)[1]
End point description:	
Intracranial ORR is defined as the percentage of participants with either a complete response (CR) or a partial response (PR) in their intracranial disease based on two consecutive assessments >= 4 weeks	

apart. Disease status for this endpoint will be determined by an Independent Review Committee (IRC) in accordance with Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) with modified measurability definition for intracranial lesions (>= 0.5 cm by MRI) and allowing up to five intracranial target lesions. CR is defined as disappearance of all lesions. PR is defined as >=30% decrease in tumor burden, in the absence of CR. The primary endpoint is analyzed on the BRAFV600 mutation positive (Cohort 2) only as the Sponsor had discontinued enrolment into Cohort 1. The evaluable population included all enrolled participants who received study medication and had at least two post-baseline intracranial tumour assessments for response evaluation.

End point type	Primary

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

Notes:

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

End point values	Evaluable Population: Cohort 2			
Subject group type	Subject analysis set			
Number of subjects analysed	56			
Units: Percentage of participants				
number (confidence interval 95%)	46.4 (32.99 to 60.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

Intracranial, extracranial and overall PFS defined as the time from study treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1.

The safety population included all participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

End point values	Cohort 1- cobimetinib and atezolizumab	Cohort 2 - cobimetinib, atezolizumab and vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	65		
Units: Months				
median (confidence interval 95%)				
Intracranial	2.17 (1.74 to 7.98)	5.78 (5.36 to 7.43)		

Extracranial	4.21 (1.84 to 12.65)	10.68 (7.85 to 13.67)		
Overall	1.81 (1.71 to 3.71)	5.49 (5.13 to 7.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall ORR

End point title	Overall ORR

End point description:

Overall ORR, defined as the percentage of participants with either a CR or PR in their overall disease (i.e. including intracranial and extracranial disease) based on two consecutive assessments >= 4 weeks apart, as determined by the investigator according to RECIST v1.1. CR was defined as disappearance of all target and non-target lesions and (if applicable) normalization of tumor marker levels. PR was defined as at least a 30 percent (%) decrease in sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR.

The safety population included all participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

End point values	Cohort 1- cobimetinib and atezolizumab	Cohort 2 - cobimetinib, atezolizumab and vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	65		
Units: Percentage of participants				
number (confidence interval 95%)	26.7 (7.79 to 55.10)	52.3 (39.54 to 64.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Extracranial ORR

End point title	Extracranial ORR

End point description:

Extracranial ORR, defined as the percentage of participants with either a CR or PR in their extracranial disease based on two consecutive assessments >=4 weeks apart, as determined by the investigator according to RECIST v1.1.

The safety population included all participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

End point values	Cohort 1- cobimetinib and atezolizumab	Cohort 2 - cobimetinib, atezolizumab and vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	65		
Units: Percentage of participants				
number (confidence interval 95%)	20.0 (4.33 to 48.09)	56.9 (44.04 to 69.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)[2]

End point description:

Intracranial, extracranial and overall DCR, defined as the percentage of participants with a CR or PR or stable disease (SD) at 16 weeks from study treatment initiation, as determined by the investigator according to RECIST v1.1. CR was defined as disappearance of all target and non-target lesions and (if applicable) normalization of tumor marker levels. PR was defined as at least a 30 percent (%) decrease in sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. SD is defined as neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for disease progression. Disease progression is defined as >=20% increase in tumor burden. This endpoint is analyzed on the BRAFV600 mutation positive (Cohort 2) only as the Sponsor had discontinued enrolment into Cohort 1. The safety population included all participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

At 16 weeks

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 analyzed on the BRAFV600 mutation positive (Cohort 2) only as the Sponsor had discontinued enrolment into Cohort 1. Data for Cohort 1 was not collected nor analyzed for this outcome measure.

End point values	Cohort 2 - cobimetinib, atezolizumab and vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Percentage of participants				
number (confidence interval 95%)				
Intracranial	50.8 (38.07 to 63.40)			

Extracranial	50.8 (38.07 to 63.40)			
Overall	50.8 (38.07 to 63.40)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)[3]

End point description:

Intracranial, extracranial and overall DOR, defined as the time from the first occurrence of a documented objective response based on two consecutive assessments ≥ 4 weeks apart to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1. This endpoint is analyzed on the BRAFV600 mutation positive (Cohort 2) only as the Sponsor had discontinued enrolment into Cohort 1. Data for Cohort 1 was not collected nor analyzed for this outcome measure.

The safety population included all participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is analyzed on the BRAFV600 mutation positive (Cohort 2) only as the Sponsor had discontinued enrolment into Cohort 1. Data for Cohort 1 was not collected nor analyzed for this outcome measure.

End point values	Cohort 2 - cobimetinib, atezolizumab and vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Months				
median (confidence interval 95%)				
Intracranial (n=32)	6.7 (5.6 to 9.5)			
Extracranial (n=37)	11.6 (9.2 to 13.0)			
Overall (n=34)	7.4 (5.5 to 9.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)[4]

End point description:

OS is defined as the time from study treatment initiation to death from any cause. The safety population

included all participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to 4 years, 4 months

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is analyzed on the BRAFV600 mutation positive (Cohort 2) only as the Sponsor had discontinued enrolment into Cohort 1. Data for Cohort 1 was not collected nor analyzed for this outcome measure.

End point values	Cohort 2 - cobimetinib, atezolizumab and vemurafenib			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Months				
median (confidence interval 95%)	13.40 (10.68 to 16.92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cognitive Symptom Deterioration

End point title	Time to Cognitive Symptom Deterioration

End point description:

Time from study treatment initiation to cognitive symptom deterioration, defined as a change (≥ 10 points on a 0-100 scale) on selected scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-BN20) (visual disorder, motor dysfunction, communication deficit, headaches, seizures and drowsiness). 9999999 = Insufficient number of participants with event.

The PRO-evaluable population included all participants who received any amount of any study medication (e.g., atezolizumab, cobimetinib, or vemurafenib) and had a baseline and at least one post baseline PRO assessment in the questionnaire of interest (EORTC QLQ-C30 or EORTC QLQBN20).

End point type	Secondary

End point timeframe:

Up to 48 months

End point values	PRO-evaluable Population: Cohort 1	PRO-evaluable Population: Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	63		
Units: Months				
median (confidence interval 95%)				
Visual Disorder	3.75 (1.87 to 9999999)	2.99 (1.41 to 8.74)		

Motor Dysfunction	1.87 (1.08 to 19.84)	6.70 (3.94 to 13.90)		
Communication Deficit	6.44 (2.83 to 9999999)	13.90 (6.54 to 21.13)		
Headaches	9999999 (1.08 to 9999999)	10.84 (5.55 to 9999999)		
Seizures	8.31 (8.31 to 9999999)	9999999 (17.74 to 9999999)		
Drowsiness	2.83 (1.08 to 9999999)	7.16 (1.94 to 9999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptom and Function Deterioration

End point title	Time to Symptom and Function Deterioration

End point description:

Time from study treatment initiation to symptom and function deterioration defined as a change (≥ 10 points on a 0-100 scale) in fatigue, physical functioning, cognitive functioning, or role functioning as measured by the Fatigue, Physical, Cognitive, Role Functioning scales of the EORTC QLQ-C30. 9999999 = Insufficient number of participants with event

The PRO-evaluable population included all participants who received any amount of any study medication (e.g., atezolizumab, cobimetinib, or vemurafenib) and had a baseline and at least one post baseline PRO assessment in the questionnaire of interest (EORTC QLQ-C30 or EORTC QLQBN20).

End point type	Secondary

End point timeframe:

Up to 48 months

End point values	PRO-evaluable Population: Cohort 1	PRO-evaluable Population: Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	63		
Units: Months				
median (confidence interval 95%)				
Physical Functioning	9999999 (0.99 to 9999999)	11.56 (5.55 to 9999999)		
Cognitive Functioning	11.99 (1.91 to 9999999)	8.25 (5.55 to 9999999)		
Role Functioning	2.83 (1.35 to 6.47)	4.07 (1.61 to 6.47)		
Fatigue	1.35 (0.95 to 9999999)	1.45 (1.38 to 6.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Stable/Improved Health-related Quality of Life (HRQoL) Scores

End point title	Duration of Stable/Improved Health-related Quality of Life (HRQoL) Scores

End point description:

Duration of Stable/Improved HRQoL scores as assessed through use of the two-item Global Health Status (GHS)/HRQoL subscale (Questions 29 and 30) of the EORTC QLQ-C30. 9999999 = Insufficient number of participants with event.

The PRO-evaluable population included all participants who received any amount of any study medication (e.g., atezolizumab, cobimetinib, or vemurafenib) and had a baseline and at least one post baseline PRO assessment in the questionnaire of interest (EORTC QLQ-C30 or EORTC QLQBN20).

End point type	Secondary

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

End point values	PRO-evaluable Population: Cohort 1	PRO-evaluable Population: Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	63		
Units: Months				
median (confidence interval 95%)	9999999 (15.21 to 9999999)	6.14 (3.68 to 10.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events

End point title	Percentage of Participants with Adverse Events

End point description:

The safety profile of Cobimetinib plus Atezolizumab and Cobimetinib plus Atezolizumab plus Vemurafenib is evaluated in terms of occurrence and severity of AEs. Severity will be determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0)

The safety population included all participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to 4 years, 4 months

End point values	Safety-evaluable Population: Cohort 1	Safety-evaluable Population: Cohort 2	Safety-evaluable Population: Cohort 2 (no atezolizumab)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	60	5	
Units: Percentage of participants				
number (not applicable)				
Occurrence (n=15,60,5)	100	100	100	
Grade 1 (n=1,1,0)	6.7	1.7	0	
Grade 2 (n=3,13,1)	20.0	21.7	20.0	
Grade 3 (n=9,35,2)	60.0	58.3	40.0	
Grade 4 (n=1,10,0)	6.7	16.7	0	
Grade 5 (n=1,1,2)	6.7	1.7	40.0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 4 years, 4 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Cohort 1- Cobimetinib and Atezolizumab
Reporting group description:	
Participants with BRAFV600 wild-type disease will be administered cobimetinib on Days 1-21 of each 28-day cycle; and atezolizumab on Days 1 and 15 of each treatment cycle.	
Reporting group title	Cohort 2 - Cobimetinib and Vemurafenib
Reporting group description:	
There were 5 participants in Cohort 2 administered with cobimetinib and vemurafenib only as they dropped out during the run-in period.	
Reporting group title	Cohort 2 - Cobimetinib, Atezolizumab and Vemurafenib
Reporting group description:	
Participants with BRAFV600 mutation-positive disease will be administered cobimetinib, atezolizumab and vemurafenib in 28-day treatment cycles. Treatment includes a 28-day run-in period where participants will receive cobimetinib and vemurafenib only. Upon completion of the 28-day run-in period, atezolizumab will be added to their treatment regimen	

Serious adverse events	Cohort 1- Cobimetinib and Atezolizumab	Cohort 2 - Cobimetinib and Vemurafenib	Cohort 2 - Cobimetinib, Atezolizumab and Vemurafenib
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)	5 / 5 (100.00%)	21 / 60 (35.00%)
number of deaths (all causes)	11	3	47
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal adenoma			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
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 disorders			

Thrombophlebitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (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
Death			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (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
Oedema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
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 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (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
Myocarditis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limbic encephalitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			

subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
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			
Pancytopenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
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			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (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

Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (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
Gallbladder rupture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 5 (20.00%)	0 / 60 (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
Drug-induced liver injury			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
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 morbilliform			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (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 maculo-papular			
subjects affected / exposed	0 / 15 (0.00%)	1 / 5 (20.00%)	0 / 60 (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
Photosensitivity reaction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pustular psoriasis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
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			
subjects affected / exposed	0 / 15 (0.00%)	1 / 5 (20.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 15 (0.00%)	1 / 5 (20.00%)	0 / 60 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
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			
Muscular weakness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
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 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	2 / 60 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			

subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
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 diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 15 (0.00%)	1 / 5 (20.00%)	0 / 60 (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
Appendicitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (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

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

Non-serious adverse events	Cohort 1- Cobimetinib and Atezolizumab	Cohort 2 - Cobimetinib and Vemurafenib	Cohort 2 - Cobimetinib, Atezolizumab and Vemurafenib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	4 / 5 (80.00%)	60 / 60 (100.00%)
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1
Hypertension			
subjects affected / exposed	2 / 15 (13.33%)	0 / 5 (0.00%)	10 / 60 (16.67%)
occurrences (all)	2	0	12
Deep vein thrombosis			

subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 15 (26.67%)	0 / 5 (0.00%)	19 / 60 (31.67%)
occurrences (all)	5	0	23
Mass			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	3
Mucosal inflammation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	6 / 60 (10.00%)
occurrences (all)	1	0	12
Malaise			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	3 / 15 (20.00%)	1 / 5 (20.00%)	26 / 60 (43.33%)
occurrences (all)	5	1	56
Fatigue			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	4 / 60 (6.67%)
occurrences (all)	1	0	4
Oedema peripheral			
subjects affected / exposed	2 / 15 (13.33%)	0 / 5 (0.00%)	8 / 60 (13.33%)
occurrences (all)	3	0	9
Xerosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 5 (20.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			

Contrast media allergy			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	4 / 60 (6.67%)
occurrences (all)	1	0	4
Pneumonitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	6 / 60 (10.00%)
occurrences (all)	1	0	6
Oropharyngeal pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences (all)	2	0	1
Cough			
subjects affected / exposed	2 / 15 (13.33%)	0 / 5 (0.00%)	4 / 60 (6.67%)
occurrences (all)	2	0	4
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Insomnia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	5 / 60 (8.33%)
occurrences (all)	0	0	6
Investigations			
Blood magnesium decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Ejection fraction decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1

Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	11 / 60 (18.33%)
occurrences (all)	0	0	13
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 15 (13.33%)	0 / 5 (0.00%)	14 / 60 (23.33%)
occurrences (all)	2	0	21
Amylase increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	19 / 60 (31.67%)
occurrences (all)	0	0	27
Blood creatinine increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	9 / 60 (15.00%)
occurrences (all)	0	0	12
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 15 (13.33%)	0 / 5 (0.00%)	28 / 60 (46.67%)
occurrences (all)	31	0	78
Thyroxine free increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	5 / 60 (8.33%)
occurrences (all)	0	0	5
Lipase increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	23 / 60 (38.33%)
occurrences (all)	0	0	45
Alanine aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	13 / 60 (21.67%)
occurrences (all)	1	0	26
Tri-iodothyronine free decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	4
Transaminases increased			

subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	5
Lymphocyte count decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Blood bilirubin increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	4 / 60 (6.67%)
occurrences (all)	1	0	9
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Mitral valve incompetence			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Myocardial infarction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 15 (13.33%)	0 / 5 (0.00%)	8 / 60 (13.33%)
occurrences (all)	6	0	13
Dizziness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Dysgeusia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	6 / 60 (10.00%)
occurrences (all)	1	0	6
Seizure			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	4
Sciatica			

subjects affected / exposed	2 / 15 (13.33%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	2	0	0
Tremor			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Anaemia			
subjects affected / exposed	4 / 15 (26.67%)	1 / 5 (20.00%)	11 / 60 (18.33%)
occurrences (all)	5	1	11
Eosinophilia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 5 (20.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Lymphopenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 15 (0.00%)	1 / 5 (20.00%)	2 / 60 (3.33%)
occurrences (all)	0	1	2
Vision blurred			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	5 / 60 (8.33%)
occurrences (all)	0	0	5
Keratitis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 5 (20.00%)	0 / 60 (0.00%)
occurrences (all)	1	1	0
Visual impairment			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1
Eye pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 5 (20.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Uveitis			

subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	4
Serous retinopathy			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	8 / 60 (13.33%)
occurrences (all)	0	0	9
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	5
Serous retinal detachment			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	1	0	3
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	6 / 60 (10.00%)
occurrences (all)	1	0	7
Mouth ulceration			
subjects affected / exposed	0 / 15 (0.00%)	1 / 5 (20.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	6 / 15 (40.00%)	0 / 5 (0.00%)	29 / 60 (48.33%)
occurrences (all)	17	0	60
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	7 / 60 (11.67%)
occurrences (all)	1	0	8
Vomiting			
subjects affected / exposed	2 / 15 (13.33%)	1 / 5 (20.00%)	10 / 60 (16.67%)
occurrences (all)	4	1	15
Stomatitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	5 / 60 (8.33%)
occurrences (all)	0	0	5
Gastritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Odynophagia			

subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	4
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Nausea			
subjects affected / exposed	2 / 15 (13.33%)	0 / 5 (0.00%)	14 / 60 (23.33%)
occurrences (all)	2	0	22
Dry mouth			
subjects affected / exposed	1 / 15 (6.67%)	1 / 5 (20.00%)	4 / 60 (6.67%)
occurrences (all)	1	1	4
Abdominal pain upper			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	5 / 60 (8.33%)
occurrences (all)	1	0	6
Dyspepsia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	6 / 60 (10.00%)
occurrences (all)	0	0	6
Gastrointestinal disorder			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 5 (20.00%)	1 / 60 (1.67%)
occurrences (all)	1	1	1
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	11 / 60 (18.33%)
occurrences (all)	0	0	16
Rash			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	20 / 60 (33.33%)
occurrences (all)	1	0	29
Vitiligo			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	4
Alopecia			

subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	5 / 60 (8.33%)
occurrences (all)	0	0	5
Rash follicular			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1
Rash maculo-papular			
subjects affected / exposed	2 / 15 (13.33%)	1 / 5 (20.00%)	17 / 60 (28.33%)
occurrences (all)	2	1	20
Dermatitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Erythema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	1	0	5
Scab			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			
subjects affected / exposed	4 / 15 (26.67%)	0 / 5 (0.00%)	18 / 60 (30.00%)
occurrences (all)	9	0	21
Pruritus			
subjects affected / exposed	2 / 15 (13.33%)	1 / 5 (20.00%)	9 / 60 (15.00%)
occurrences (all)	2	1	9
Hyperkeratosis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	5
Dermatitis allergic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Endocrine disorders			
Hyperthyroidism			

subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	1	0	3
Hypothyroidism			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	8 / 60 (13.33%)
occurrences (all)	1	0	8
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	11 / 60 (18.33%)
occurrences (all)	0	0	16
Arthralgia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 5 (20.00%)	19 / 60 (31.67%)
occurrences (all)	2	1	24
Pain in extremity			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	4 / 60 (6.67%)
occurrences (all)	1	0	4
Sjogren's syndrome			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	6 / 60 (10.00%)
occurrences (all)	0	0	6
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	1	0	3
Fungal skin infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	0 / 15 (0.00%)	1 / 5 (20.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	4
Furuncle			

subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Influenza			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	5
Rhinitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1
Rash pustular			
subjects affected / exposed	2 / 15 (13.33%)	0 / 5 (0.00%)	2 / 60 (3.33%)
occurrences (all)	2	0	3
Respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1
Folliculitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 5 (0.00%)	2 / 60 (3.33%)
occurrences (all)	2	0	2
Hypoproteinaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Vitamin D deficiency			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	4 / 60 (6.67%)
occurrences (all)	1	0	4

Iron deficiency			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	5 / 60 (8.33%)
occurrences (all)	0	0	5
Cell death			
subjects affected / exposed	0 / 15 (0.00%)	1 / 5 (20.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	6 / 60 (10.00%)
occurrences (all)	0	0	6
Hyperglycaemia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 5 (20.00%)	7 / 60 (11.67%)
occurrences (all)	1	1	11
Hyponatraemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 5 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Hyperkalaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 5 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2018	The following updates were made: [1] The Roche Medical Responsible was identified as the Roche Medical Monitor; [2] Descriptions of the roles and responsibilities on the Internal Monitoring Committee were added; [3] Requirements for re-screening were added and/or clarified; [4] Eligibility requirement for woman of childbearing potential to refrain from donating eggs was added; [5] Text clarifying that the eligibility requirements for men refraining from donating sperm were added; [6] Text identifying acetaminophen as CYP1A2 was added to clarify its interaction with vemurafenib; [7] Text describing and allowing screening window extensions was added; [8] Text describing Next-generation sequencing of study participant samples was revised; [9] Timing of destruction of samples collected from participants who have not consented to optional donation was modified; [10] Nephritis was added as a known risk to be associated with atezolizumab; [11] The length of time atezolizumab treatment was suspended was revised; [12] Submission of tumor tissue biomarker analyses was moved from screening to Cycle 1, Day 1; [13] [9] Additional minor changes were made to improve clarity and consistency.
12 August 2019	The following updates were made: [1] The Sponsor communicated the decision to discontinue enrollment in Cohort 1 in a Dear Investigator Letter dated 9 July 2019; [2] Benefit-Risk assessment was updated; [3] Sample size calculations were revised; [4] Primary efficacy analysis was revised to only include participants enrolled in Cohort 2; [5] Intracranial ORR as assessed by the investigator according to RECIST v1.1 was added as a secondary efficacy endpoint; [6] Inclusion criteria was revised; [7] Study Treatment Dosage for Cohort 1 was updated; [8] Permitted Therapy section was updated; [9] Guidelines for managing patients who experienced atezolizumab-associated adverse events were revised; [10] Management Guidelines for Cohort 1 and Emergency Medical Contacts were updated; [11] Abortions section was revise to clarify new safety reporting requirements; [12] Immune-related was changed to 'immune-mediated' throughout the protocol; [13] Additional minor changes were made to improve the clarity and consistency.
26 February 2020	The following updates were made: [1] The definition of the endpoint of intracranial ORR by investigator was clarified to align with the IRC-determined definition; [2] Proteinuria inclusion criteria was removed; [3] The rationale for the dose of atezolizumab was updated; [4] Clarity was introduced on the recommendation for vemurafenib interruption in the event of planned stereotactic radiotherapy; [5] Clarification that intracranial and extracranial tumour assessments do not need to be done for study purposes; [6] In the event of disease progression, a confirmatory tumour assessment was to be performed approximately four weeks later; [7] Added "Management of Study Quality" section and updated the "Publication of Data and Protection of Trade Secrets" section; [8] Safety updates from the atezolizumab Investigator's Brochure were added; [9] Additional minor changes were made to improve clarity and consistency.

04 March 2022	The following updates were made: [1] List of approved indications for atezolizumab was updated; [2] Provisions related to performing the study in the setting of the coronavirus disease 2019 (COVID-19) pandemic were added; [3] Benefit-risk assessment and guidance on concomitant administration of COVID-19 vaccines with atezolizumab was added; [4] AE management guidelines were updated; [5] The responsibilities of the investigator and the role of the Medical Monitor were clarified; [6] Language was added to indicate that sites could confirm that appropriate temperature conditions were maintained during investigational medicinal product (IMP) transit; [7] Immunosuppressive medications have been removed from the prohibited therapy section and added to the cautionary therapy section; [8] Updates related to the risks associated with atezolizumab; [9] Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) replaced systemic inflammatory response syndrome on the list of atezolizumab-associated adverse events ofspecial interest (AESI); [10] Language was added to the ICF to instruct female participants to inform the investigator if they became pregnant; [11] language regarding investigator reporting of pregnancies was clarified; [12] Management guidelines for Grade 4 myositis were removed; [13] The management guidelines for HLH and MAS have been modified to indicate that HLH were to be considered when CRS presentation was atypical or prolonged, to add anticytokine therapy as an option for treating HLH or MAS, and suggest that published guidelines be followed for HLH or MAS events that did not respond to treatment within 24 hours; [14] Minor updates to the management guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome; [15] The medical term “primary biliary cirrhosis” was replaced by the term “primary biliary cholangitis;” [16] Additional minor changes were made to improve clarity and consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The Sponsor decided to discontinue enrollment into Cohort 1, which was communicated in a Dear Investigator Letter dated 9 July 2019.

Notes: