Clinical trial results:
A Phase III, Open-Label, Multicenter, Three-Arm, Randomized Study to Investigate the Efficacy and Safety of Cobimetinib Plus Atezolizumab and Atezolizumab Monotherapy vs. Regorafenib in Patients With Previously Treated Unresectable Locally Advanced or Metastatic Colorectal Adenocarcinoma.

Summary

EudraCT number	2016-000202-11
Trial protocol	GB BE DE IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	24 March 2019
First version publication date	24 March 2019

Trial information

Trial identification

Sponsor protocol code	GO30182

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02788279
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	Interim
Date of interim/final analysis	09 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 March 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of cobimetinib plus atezolizumab compared to regorafenib on the basis of overall survival (OS). Atezolizumab monotherapy will also be evaluated compared to regorafenib on the basis of OS.

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	05 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Italy: 59
Country: Number of subjects enrolled	Korea, Republic of: 32
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	United States: 108
Worldwide total number of subjects	363
EEA total number of subjects	160

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	255
From 65 to 84 years	107
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 490 participants were screened of whom only 363 participants were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Regorafenib

Arm description:

Participants will receive regorafenib 160 mg orally on Days 1 to 21 in a 28-day cycle until disease progression according to RECIST Version 1.1, unacceptable toxicity, death, participant's or physician decision to withdraw, or pregnancy, whichever occurs first.

Arm type	Active comparator
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	
Other name	Stivarga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 160 mg orally once daily on Days 1 to 21 in a 28-day cycle.

Arm title	Cobimetinib + Atezolizumab

Arm description:

Participants will receive cobimetinib 60 mg orally on Days 1 to 21 plus atezolizumab 840 mg IV on Day 1 and Day 15 in a 28-day cycle until disease progression according to RECIST Version 1.1, unacceptable toxicity, death, participant's or physician decision to withdraw, or pregnancy, whichever occurs first.

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

Dosage and administration details:

Participants received 840 mg IV on Day 1 and Day 15 in a 28-day cycle.

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

Dosage and administration details:

Participants received 60 mg (three tablets of 20 mg each)
orally once daily for Days 1 to 21 in a 28-day cycle.

Arm title	Atezolizumab

Arm description:

Participants will receive atezolizumab monotherapy 1200 milligrams (mg) intravenous (IV) on Day 1 in a 21-day cycle until disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, unacceptable toxicity, death, participant's or physician decision to withdraw, or pregnancy, whichever occurs first.

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

Dosage and administration details:

Participants received a single dose of 1200 mg IV on Day 1 in a 21-day cycle.

Number of subjects in period 1	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab
Started	90	183	90
Received treatment (Safety Population)	80	179	90
Modified ITT population	57	125	61
Completed	0	0	0
Not completed	90	183	90
Adverse event, serious fatal	57	125	65
Still on study	24	43	18
Consent withdrawn by subject	9	12	5
Lost to follow-up	-	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Regorafenib
Reporting group description:	
Participants will receive regorafenib 160 mg orally on Days 1 to 21 in a 28-day cycle until disease progression according to RECIST Version 1.1, unacceptable toxicity, death, participant's or physician decision to withdraw, or pregnancy, whichever occurs first.	
Reporting group title	Cobimetinib + Atezolizumab
Reporting group description:	
Participants will receive cobimetinib 60 mg orally on Days 1 to 21 plus atezolizumab 840 mg IV on Day 1 and Day 15 in a 28-day cycle until disease progression according to RECIST Version 1.1, unacceptable toxicity, death, participant's or physician decision to withdraw, or pregnancy, whichever occurs first.	
Reporting group title	Atezolizumab
Reporting group description:	
Participants will receive atezolizumab monotherapy 1200 milligrams (mg) intravenous (IV) on Day 1 in a 21-day cycle until disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, unacceptable toxicity, death, participant's or physician decision to withdraw, or pregnancy, whichever occurs first.	

Reporting group values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab
Number of subjects	90	183	90
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)	62	125	68
From 65-84 years	28	57	22
85 years and over	0	1	0
Age Continuous Units: Years			
arithmetic mean	58.4	58.0	56.7
standard deviation	± 10.3	± 11.9	± 11.1
Sex: Female, Male Units: Subjects			
Female	39	76	31
Male	51	107	59
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	12	18	11
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	0	8	2
White	71	152	73
More than one race	0	0	0

Unknown or Not Reported	7	4	3
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	9	11	5
Not Hispanic or Latino	77	166	82
Unknown or Not Reported	4	6	3

Reporting group values	Total		
Number of subjects	363		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	255		
From 65-84 years	107		
85 years and over	1		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	146		
Male	217		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	41		
Native Hawaiian or Other Pacific Islander	2		
Black or African American	10		
White	296		
More than one race	0		
Unknown or Not Reported	14		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	25		
Not Hispanic or Latino	325		
Unknown or Not Reported	13		

End points

End points reporting groups

Reporting group title	Regorafenib
Reporting group description:	
Participants will receive regorafenib 160 mg orally on Days 1 to 21 in a 28-day cycle until disease progression according to RECIST Version 1.1, unacceptable toxicity, death, participant's or physician decision to withdraw, or pregnancy, whichever occurs first.	
Reporting group title	Cobimetinib + Atezolizumab
Reporting group description:	
Participants will receive cobimetinib 60 mg orally on Days 1 to 21 plus atezolizumab 840 mg IV on Day 1 and Day 15 in a 28-day cycle until disease progression according to RECIST Version 1.1, unacceptable toxicity, death, participant's or physician decision to withdraw, or pregnancy, whichever occurs first.	
Reporting group title	Atezolizumab
Reporting group description:	
Participants will receive atezolizumab monotherapy 1200 milligrams (mg) intravenous (IV) on Day 1 in a 21-day cycle until disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, unacceptable toxicity, death, participant's or physician decision to withdraw, or pregnancy, whichever occurs first.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall survival is defined as the time (in months) between the date of randomization and the date of death due to any cause. Participants who were not reported as having died at the date of analysis were censored at the date when they were last known to be alive. Participants who did not have post-baseline information were censored at the date of randomization + 1 day. Median OS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley.	
End point type	Primary
End point timeframe:	
From randomization up to death due to any cause (up to approximately 20 months or data cutoff of 09-Mar-2018)	

End point values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	183	90	
Units: months				
median (confidence interval 95%)	8.51 (6.41 to 10.71)	8.87 (7.00 to 10.61)	7.10 (6.05 to 10.05)	

Statistical analyses

Statistical analysis title	Cobimetinib + Atezolizumab vs. Regorafenib
Comparison groups	Regorafenib v Cobimetinib + Atezolizumab

Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9871
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.38

Statistical analysis title	Atezolizumab vs. Regorafenib
Comparison groups	Regorafenib v Atezolizumab
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.336
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.71

Statistical analysis title	Cobimetinib + Atezolizumab vs. Regorafenib
Comparison groups	Regorafenib v Cobimetinib + Atezolizumab
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9686
Method	Unstratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.38

Statistical analysis title	Atezolizumab vs. Regorafenib

Comparison groups	Regorafenib v Atezolizumab
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3553
Method	Unstratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.69

Secondary: Progression-Free Survival (PFS) as Determined by the Investigator According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point title	Progression-Free Survival (PFS) as Determined by the Investigator According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point description:

PFS was defined as the time from randomization to disease progression as determined by the investigator with the use of RECIST v1.1 or death due to any cause, whichever occurred earlier. Disease progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimeters (mm). For non-target lesions, disease progression was defined as unequivocal progression of existing lesions. The appearance of one or more new lesions was also considered progression. Participants who did not have post-baseline information were censored at the date of randomization + 1 day. Median OS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley.

End point type	Secondary

End point timeframe:

From randomization up to disease progression or death due to any cause (up to approximately 20 months or data cutoff of 09-Mar-2018)

End point values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	183	90	
Units: months				
median (confidence interval 95%)	2.00 (1.87 to 3.61)	1.91 (1.87 to 1.97)	1.94 (1.91 to 2.10)	

Statistical analyses

Statistical analysis title	Cobimetinib + Atezolizumab vs. Regorafenib
Comparison groups	Regorafenib v Cobimetinib + Atezolizumab

Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1208
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.65

Statistical analysis title	Atezolizumab vs. Regorafenib
Comparison groups	Regorafenib v Atezolizumab
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0509
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.94

Statistical analysis title	Cobimetinib + Atezolizumab vs. Regorafenib
Comparison groups	Regorafenib v Cobimetinib + Atezolizumab
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1726
Method	Unstratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.6

Statistical analysis title	Atezolizumab vs. Regorafenib

Comparison groups	Regorafenib v Atezolizumab
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0467
Method	Unstratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.91

Secondary: Percentage of Participants with Investigator-Assessed Objective Response of Complete Response (CR) or Partial Response (PR) According to RECIST Version 1.1

End point title	Percentage of Participants with Investigator-Assessed Objective Response of Complete Response (CR) or Partial Response (PR) According to RECIST Version 1.1

End point description:

PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. CR was defined as disappearance of all target and non-target lesions and normalization of tumor marker levels (as applicable to non-target lesions). Objective response and its 95% CI were calculated using the Clopper-Pearson method.

End point type	Secondary

End point timeframe:

From randomization up to death due to any cause (up to approximately 20 months or data cutoff of 09-Mar-2018)

End point values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	183	90	
Units: percentage of participants				
number (confidence interval 95%)	2.2 (0.27 to 7.80)	2.7 (0.89 to 6.26)	2.2 (0.27 to 7.80)	

Statistical analyses

Statistical analysis title	Cobimetinib + Atezolizumab vs. Regorafenib
Comparison groups	Regorafenib v Cobimetinib + Atezolizumab

Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Stratified Cochrane-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.92
upper limit	4.94

Statistical analysis title	Atezolizumab vs. Regorafenib
Comparison groups	Regorafenib v Atezolizumab
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Stratified Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.89
upper limit	4.89

Secondary: Duration of Response (DOR) According to RECIST Version 1.1

End point title	Duration of Response (DOR) According to RECIST Version 1.1

End point description:

DOR is defined as the period measured from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease or death is documented. Disease progression was determined on the basis of investigator assessment with use of RECIST v1.1. Median DOR was estimated using the Kaplan-Meier method, and the 95% CI was calculated using the method of Brookmeyer and Crowley.

End point type	Secondary

End point timeframe:

From first occurrence of CR or PR up to disease progression or death due to any cause (up to approximately 20 months or data cutoff of 09-Mar-2018)

End point values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	5	2	
Units: months				
median (confidence interval 95%)	4.50 (3.61 to 5.39)	1.97 (1.77 to 3.81)	2.81 (1.84 to 3.78)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life-C30 Questionnaire (EORTC QLQ-C30) Physical Functioning Sub-scale Score

End point title	Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life-C30 Questionnaire (EORTC QLQ-C30) Physical Functioning Sub-scale Score

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions generating five functional scores (physical, role, cognitive, emotional, and social); a global health status/global quality of life scale score; three symptom scale scores (fatigue, pain, and nausea and vomiting); and six stand alone one-item scores that capture additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) and perceived financial burden. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning.

End point type	Secondary

End point timeframe:

From randomization up to data cutoff of 09-Mar-2018 (up to approximately 20 months)

End point values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[1]	0[2]	0[3]	
Units: units of a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[1] - The results will be provided at the time of final results disclosure in December 2019.

[2] - The results will be provided at the time of final results disclosure in December 2019.

[3] - The results will be provided at the time of final results disclosure in December 2019.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life-C30 Questionnaire (EORTC QLQ-C30) Global Quality of Life Sub-scale Score at the End of the Study

End point title	Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life-C30 Questionnaire (EORTC QLQ-C30) Global Quality of Life Sub-scale Score at the

	End of the Study

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions generating five functional scores (physical, role, cognitive, emotional, and social); a global health status/global quality of life scale score; three symptom scale scores (fatigue, pain, and nausea and vomiting); and six stand alone one-item scores that capture additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) and perceived financial burden. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning.

End point type	Secondary

End point timeframe:

Baseline, end of the study (up to approximately 3 years)

End point values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[4]	0[5]	0[6]	
Units: units of a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[4] - The results will be provided at the time of final results disclosure in December 2019.

[5] - The results will be provided at the time of final results disclosure in December 2019.

[6] - The results will be provided at the time of final results disclosure in December 2019.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events (AEs)

End point title	Percentage of Participants with Adverse Events (AEs)

End point description:

End point type	Secondary

End point timeframe:

Baseline up to approximately data cutoff of 09-Mar-2018 (approximately 20 months)

End point values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	179	90	
Units: percentage of participants				
number (not applicable)	97.5	99.4	92.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Cobimetinib

End point title	Plasma Concentration of Cobimetinib

End point description:

End point type	Secondary

End point timeframe:

Predose (0 hours) and 3 to 6 hours after dose on Day 15 of Cycles 1 and 4 (1 cycle = 28 days)

End point values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[7]	0[8]	0[9]	
Units: ng/mL				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[7] - The results will be provided at the time of final results disclosure in December 2019.

[8] - The results will be provided at the time of final results disclosure in December 2019.

[9] - The results will be provided at the time of final results disclosure in December 2019.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Atezolizumab

End point title	Serum Concentration of Atezolizumab

End point description:

Pre-infusion (0 hours) on Day 1 of Cycles 1 to 4; 30 minutes post-infusion on Day 1 of Cycles 1 and 4; pre-infusion (0 hours) on Day 1 of Cycle 8 and every 8 cycles thereafter; at treatment discontinuation; 120 days after treatment discontinuation (up to approximately 3 years) (1 cycle = 28 days)

End point type	Secondary

End point timeframe:

Pre-infusion (0 hours) on Day 1 of Cycle 1 up to approximately 3 years. Detailed time frame is explained in the outcome measure description field.

End point values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[10]	0[11]	0[12]	
Units: ng/mL				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[10] - The results will be provided at the time of final results disclosure in December 2019.

[11] - The results will be provided at the time of final results disclosure in December 2019.

[12] - The results will be provided at the time of final results disclosure in December 2019.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) to Atezolizumab

End point title	Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) to Atezolizumab

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion (0 hours) on Day 1 of Cycles 1 to 4, 8, and every 8 cycles thereafter; at treatment discontinuation; 120 days after treatment discontinuation (up to approximately 3 years) (1 cycle = 28 days)

End point values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[13]	0[14]	0[15]	
Units: percentage of participants				
number (not applicable)				

Notes:

[13] - The results will be provided at the time of final results disclosure in December 2019.

[14] - The results will be provided at the time of final results disclosure in December 2019.

[15] - The results will be provided at the time of final results disclosure in December 2019.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to clinical cut-off of 09-Mar-2018 (approximately 20 months).

Adverse event reporting additional description:

The safety analysis set (SAF) included all enrolled participants, who received at least one dose of any study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Atezolizumab

Reporting group description:

Participants will receive atezolizumab monotherapy 1200 milligrams (mg) intravenous (IV) on Day 1 in a 21-day cycle until disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, unacceptable toxicity, death, participant's or physician decision to withdraw, or pregnancy, whichever occurs first.

Reporting group title	Regorafenib

Reporting group description:

Participants will receive regorafenib 160 mg orally on Days 1 to 21 in a 28-day cycle until disease progression according to RECIST Version 1.1, unacceptable toxicity, death, participant's or physician decision to withdraw, or pregnancy, whichever occurs first.

Reporting group title	Cobimetinib + Atezolizumab

Reporting group description:

Participants will receive cobimetinib 60 mg orally on Days 1 to 21 plus atezolizumab 840 mg IV on Day 1 and Day 15 in a 28-day cycle until disease progression according to RECIST Version 1.1, unacceptable toxicity, death, participant's or physician decision to withdraw, or pregnancy, whichever occurs first.

Serious adverse events	Atezolizumab	Regorafenib	Cobimetinib + Atezolizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 90 (16.67%)	18 / 80 (22.50%)	71 / 179 (39.66%)
number of deaths (all causes)	65	54	123
number of deaths resulting from adverse events			
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PELVIC VENOUS THROMBOSIS			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	2 / 90 (2.22%)	2 / 80 (2.50%)	12 / 179 (6.70%)
occurrences causally related to treatment / all	1 / 2	1 / 2	12 / 15
deaths causally related to treatment / all	1 / 2	1 / 2	12 / 15
ASTHENIA			
subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	0 / 179 (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
CHILLS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
DEATH			
subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	0 / 179 (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
FATIGUE			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
INFLAMMATION			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

MUCOSAL INFLAMMATION			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Reproductive system and breast disorders			
VAGINAL HAEMORRHAGE			
subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	0 / 179 (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
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	2 / 2
PLEURAL EFFUSION			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
PNEUMONITIS			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
HYPOXIA			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PNEUMOTHORAX			

subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
DELIRIUM			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
CONFUSIONAL STATE			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Investigations			
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	2 / 2
INFLUENZA A VIRUS TEST POSITIVE			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
INTERNATIONAL NORMALISED RATIO INCREASED			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			

subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	3 / 179 (1.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	3 / 3
HIP FRACTURE			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
STOMA SITE HAEMORRHAGE			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
LEFT VENTRICULAR DYSFUNCTION			
subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	0 / 179 (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
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	0 / 179 (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
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
SYNCOPE			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
ATAXIA			

subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
COGNITIVE DISORDER			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
DIZZINESS			
subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	0 / 179 (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
ENCEPHALOPATHY			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
GUILLAIN−BARRE SYNDROME			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
METABOLIC ENCEPHALOPATHY			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
NONINFECTIVE ENCEPHALITIS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Blood and lymphatic system disorders			
ANAEMIA			

subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	5 / 179 (2.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	2 / 5
Eye disorders			
MACULOPATHY			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	0 / 90 (0.00%)	3 / 80 (3.75%)	6 / 179 (3.35%)
occurrences causally related to treatment / all	0 / 0	3 / 3	6 / 6
deaths causally related to treatment / all	0 / 0	3 / 3	6 / 6
ABDOMINAL PAIN			
subjects affected / exposed	1 / 90 (1.11%)	2 / 80 (2.50%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 2
COLITIS			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	2 / 2
INTESTINAL PERFORATION			
subjects affected / exposed	0 / 90 (0.00%)	2 / 80 (2.50%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 1
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
VOMITING			
subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
ANAL HAEMORRHAGE			

subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	0 / 179 (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
COLONIC FISTULA			
subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	0 / 179 (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
CONSTIPATION			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
ILEUS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
LOWER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	0 / 179 (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
NAUSEA			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
PANCREATITIS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
RECTAL HAEMORRHAGE			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	0 / 179 (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
SMALL INTESTINAL OBSTRUCTION			

subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	0 / 179 (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
SUBILEUS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
VOLVULUS OF SMALL BOWEL			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hepatobiliary disorders			
AUTOIMMUNE HEPATITIS			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
BILE DUCT OBSTRUCTION			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	0 / 179 (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
CHOLANGITIS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	2 / 2
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
NEPHRITIS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
STERILE PYURIA			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Endocrine disorders			
ADRENAL INSUFFICIENCY			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Musculoskeletal and connective tissue disorders			
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 2
BACK PAIN			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	0 / 179 (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
Infections and infestations			
SEPSIS			
subjects affected / exposed	0 / 90 (0.00%)	2 / 80 (2.50%)	4 / 179 (2.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 2	4 / 4
PNEUMONIA			

subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
PULMONARY SEPSIS			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
PYELONEPHRITIS			
subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
ABDOMINAL HERNIA INFECTION			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	0 / 179 (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
BACTERAEMIA			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
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 SEPSIS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
INFECTION			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
LUNG INFECTION			

subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
ORAL CANDIDIASIS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
RHINOVIRUS INFECTION			
subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
HYPONATRAEMIA			
subjects affected / exposed	0 / 90 (0.00%)	1 / 80 (1.25%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	2 / 2
DECREASED APPETITE			
subjects affected / exposed	1 / 90 (1.11%)	0 / 80 (0.00%)	0 / 179 (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
DEHYDRATION			

subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

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

Non-serious adverse events	Atezolizumab	Regorafenib	Cobimetinib + Atezolizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 90 (88.89%)	78 / 80 (97.50%)	172 / 179 (96.09%)
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	7 / 90 (7.78%)	17 / 80 (21.25%)	8 / 179 (4.47%)
occurrences (all)	7	18	9
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	6 / 90 (6.67%)	7 / 80 (8.75%)	16 / 179 (8.94%)
occurrences (all)	8	8	26
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 90 (0.00%)	2 / 80 (2.50%)	22 / 179 (12.29%)
occurrences (all)	0	3	38
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	8 / 90 (8.89%)	1 / 80 (1.25%)	13 / 179 (7.26%)
occurrences (all)	11	1	13
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	5 / 90 (5.56%)	5 / 80 (6.25%)	10 / 179 (5.59%)
occurrences (all)	5	6	17
LIPASE INCREASED			
subjects affected / exposed	1 / 90 (1.11%)	6 / 80 (7.50%)	9 / 179 (5.03%)
occurrences (all)	2	7	10
BLOOD THYROID STIMULATING HORMONE INCREASED			
subjects affected / exposed	3 / 90 (3.33%)	4 / 80 (5.00%)	3 / 179 (1.68%)
occurrences (all)	3	4	5
BLOOD BILIRUBIN INCREASED			

subjects affected / exposed	2 / 90 (2.22%)	4 / 80 (5.00%)	3 / 179 (1.68%)
occurrences (all)	2	7	3
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 90 (0.00%)	5 / 80 (6.25%)	3 / 179 (1.68%)
occurrences (all)	0	6	3
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	4 / 90 (4.44%)	25 / 80 (31.25%)	9 / 179 (5.03%)
occurrences (all)	6	31	10
Nervous system disorders			
HEADACHE			
subjects affected / exposed	11 / 90 (12.22%)	10 / 80 (12.50%)	15 / 179 (8.38%)
occurrences (all)	11	12	19
DIZZINESS			
subjects affected / exposed	0 / 90 (0.00%)	3 / 80 (3.75%)	9 / 179 (5.03%)
occurrences (all)	0	3	11
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	23 / 90 (25.56%)	37 / 80 (46.25%)	63 / 179 (35.20%)
occurrences (all)	27	45	73
PYREXIA			
subjects affected / exposed	12 / 90 (13.33%)	19 / 80 (23.75%)	52 / 179 (29.05%)
occurrences (all)	13	23	66
ASTHENIA			
subjects affected / exposed	12 / 90 (13.33%)	16 / 80 (20.00%)	37 / 179 (20.67%)
occurrences (all)	19	21	53
OEDEMA PERIPHERAL			
subjects affected / exposed	8 / 90 (8.89%)	3 / 80 (3.75%)	27 / 179 (15.08%)
occurrences (all)	9	3	32
MUCOSAL INFLAMMATION			
subjects affected / exposed	4 / 90 (4.44%)	6 / 80 (7.50%)	16 / 179 (8.94%)
occurrences (all)	6	8	19
CHILLS			
subjects affected / exposed	4 / 90 (4.44%)	4 / 80 (5.00%)	13 / 179 (7.26%)
occurrences (all)	5	4	14
FACE OEDEMA			

subjects affected / exposed	0 / 90 (0.00%)	0 / 80 (0.00%)	10 / 179 (5.59%)
occurrences (all)	0	0	12
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	5 / 90 (5.56%)	8 / 80 (10.00%)	23 / 179 (12.85%)
occurrences (all)	5	9	24
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 90 (0.00%)	2 / 80 (2.50%)	10 / 179 (5.59%)
occurrences (all)	0	2	10
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	17 / 90 (18.89%)	30 / 80 (37.50%)	113 / 179 (63.13%)
occurrences (all)	23	58	195
NAUSEA			
subjects affected / exposed	19 / 90 (21.11%)	11 / 80 (13.75%)	66 / 179 (36.87%)
occurrences (all)	23	12	92
VOMITING			
subjects affected / exposed	13 / 90 (14.44%)	7 / 80 (8.75%)	51 / 179 (28.49%)
occurrences (all)	15	8	77
ABDOMINAL PAIN			
subjects affected / exposed	13 / 90 (14.44%)	22 / 80 (27.50%)	27 / 179 (15.08%)
occurrences (all)	19	29	31
CONSTIPATION			
subjects affected / exposed	11 / 90 (12.22%)	17 / 80 (21.25%)	32 / 179 (17.88%)
occurrences (all)	12	19	39
STOMATITIS			
subjects affected / exposed	0 / 90 (0.00%)	13 / 80 (16.25%)	18 / 179 (10.06%)
occurrences (all)	0	21	18
DRY MOUTH			
subjects affected / exposed	2 / 90 (2.22%)	4 / 80 (5.00%)	9 / 179 (5.03%)
occurrences (all)	2	4	9
ABDOMINAL PAIN UPPER			
subjects affected / exposed	7 / 90 (7.78%)	2 / 80 (2.50%)	3 / 179 (1.68%)
occurrences (all)	8	2	3
DYSPEPSIA			

subjects affected / exposed	2 / 90 (2.22%)	0 / 80 (0.00%)	10 / 179 (5.59%)
occurrences (all)	2	0	10
PROCTALGIA			
subjects affected / exposed	0 / 90 (0.00%)	4 / 80 (5.00%)	2 / 179 (1.12%)
occurrences (all)	0	4	2
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	12 / 90 (13.33%)	13 / 80 (16.25%)	32 / 179 (17.88%)
occurrences (all)	12	13	34
COUGH			
subjects affected / exposed	12 / 90 (13.33%)	7 / 80 (8.75%)	29 / 179 (16.20%)
occurrences (all)	12	9	30
DYSPHONIA			
subjects affected / exposed	1 / 90 (1.11%)	19 / 80 (23.75%)	0 / 179 (0.00%)
occurrences (all)	1	27	0
EPISTAXIS			
subjects affected / exposed	0 / 90 (0.00%)	7 / 80 (8.75%)	9 / 179 (5.03%)
occurrences (all)	0	7	9
OROPHARYNGEAL PAIN			
subjects affected / exposed	2 / 90 (2.22%)	4 / 80 (5.00%)	7 / 179 (3.91%)
occurrences (all)	2	5	8
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	8 / 90 (8.89%)	19 / 80 (23.75%)	82 / 179 (45.81%)
occurrences (all)	8	21	116
DERMATITIS ACNEIFORM			
subjects affected / exposed	2 / 90 (2.22%)	2 / 80 (2.50%)	46 / 179 (25.70%)
occurrences (all)	3	2	57
PALMAR−PLANTAR			
subjects affected / exposed	1 / 90 (1.11%)	42 / 80 (52.50%)	3 / 179 (1.68%)
occurrences (all)	1	69	3
ERYTHRODYSAESTHESIA SYNDROME PRURITUS			
subjects affected / exposed	3 / 90 (3.33%)	2 / 80 (2.50%)	22 / 179 (12.29%)
occurrences (all)	3	2	25
DRY SKIN			

subjects affected / exposed	3 / 90 (3.33%)	1 / 80 (1.25%)	14 / 179 (7.82%)
occurrences (all)	3	1	14
RASH MACULO−PAPULAR			
subjects affected / exposed	1 / 90 (1.11%)	3 / 80 (3.75%)	11 / 179 (6.15%)
occurrences (all)	1	3	12
ERYTHEMA			
subjects affected / exposed	0 / 90 (0.00%)	5 / 80 (6.25%)	1 / 179 (0.56%)
occurrences (all)	0	5	1
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	6 / 90 (6.67%)	3 / 80 (3.75%)	9 / 179 (5.03%)
occurrences (all)	6	3	9
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	13 / 90 (14.44%)	8 / 80 (10.00%)	15 / 179 (8.38%)
occurrences (all)	15	10	19
ARTHRALGIA			
subjects affected / exposed	8 / 90 (8.89%)	5 / 80 (6.25%)	13 / 179 (7.26%)
occurrences (all)	8	6	13
PAIN IN EXTREMITY			
subjects affected / exposed	6 / 90 (6.67%)	6 / 80 (7.50%)	12 / 179 (6.70%)
occurrences (all)	6	7	15
MYALGIA			
subjects affected / exposed	3 / 90 (3.33%)	7 / 80 (8.75%)	9 / 179 (5.03%)
occurrences (all)	3	10	12
MUSCULOSKELETAL PAIN			
subjects affected / exposed	2 / 90 (2.22%)	4 / 80 (5.00%)	4 / 179 (2.23%)
occurrences (all)	2	4	4
MUSCLE SPASMS			
subjects affected / exposed	0 / 90 (0.00%)	4 / 80 (5.00%)	3 / 179 (1.68%)
occurrences (all)	0	4	3
Infections and infestations			
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 90 (2.22%)	4 / 80 (5.00%)	7 / 179 (3.91%)
occurrences (all)	2	8	9
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	6 / 90 (6.67%)	2 / 80 (2.50%)	4 / 179 (2.23%)
occurrences (all)	6	2	6
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	21 / 90 (23.33%)	33 / 80 (41.25%)	48 / 179 (26.82%)
occurrences (all)	27	39	54
HYPOPHOSPHATAEMIA			
subjects affected / exposed	3 / 90 (3.33%)	7 / 80 (8.75%)	10 / 179 (5.59%)
occurrences (all)	3	7	10
HYPOKALAEMIA			
subjects affected / exposed	1 / 90 (1.11%)	3 / 80 (3.75%)	12 / 179 (6.70%)
occurrences (all)	1	4	15
HYPOCALCAEMIA			
subjects affected / exposed	2 / 90 (2.22%)	5 / 80 (6.25%)	7 / 179 (3.91%)
occurrences (all)	2	5	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2016	Key changes to the protocol included: clarification on regorafenib classification as IMP/NIMP, to update data on atezolizumab and cobimetinib, and to expand the window for baseline tumor assessments.
04 May 2016	Key change to the protocol was to perform thyroid function test laboratory monitoring at Day 1 of every cycle rather than Cycle 1 Day 1 and every fourth cycle.
21 October 2016	Key changes to the protocol included: an update to the safety information for identified risks of cobimetinib and an update to the safety language for atezolizumab.
28 November 2017	Key changes to the protocol included: update to the hierarchical testing procedures for OS, PFS and ORR, removal of reference to Foundation Medicine, update to adverse events management and updates to the Medical Manager contact information and web address for Global Policy on Sharing of Clinical Trials Data.

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 results represent the data up to primary completion date (09 Mar 2018).

Notes: