



## 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	26 December 2018

#### Results information

Result version number	v2 (current)
This version publication date	19 December 2019
First version publication date	24 March 2019
Version creation reason	

#### Trial information

##### Trial identification

Sponsor protocol code	GO30182
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##### 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	Final
Date of interim/final analysis	09 March 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 December 2018
Was the trial ended prematurely?	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 months)	0
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
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<b>Arm title</b>	Regorafenib
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Arm description:

Participants received regorafenib 160 mg orally once daily 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 (four tablets of 40 mg each) orally once daily on Days 1 to 21 in a 28-day cycle.

<b>Arm title</b>	Cobimetinib + Atezolizumab
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Arm description:

Participants received 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	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.

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.

<b>Arm title</b>	Atezolizumab
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**Arm description:**

Participants received atezolizumab monotherapy 1200 milligrams (mg) intravenous (IV) on Day 1 in a 21-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 a single dose of 1200 mg IV on Day 1 in a 21-day cycle.

<b>Number of subjects in period 1</b>	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
Consent withdrawn by subject	10	15	5
Death	62	136	72
Sponsor decision	18	29	11
Lost to follow-up	-	3	2

## Baseline characteristics

### Reporting groups

Reporting group title	Regorafenib
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Reporting group description:

Participants received regorafenib 160 mg orally once daily 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
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Reporting group description:

Participants received 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
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Reporting group description:

Participants received atezolizumab monotherapy 1200 milligrams (mg) intravenous (IV) on Day 1 in a 21-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 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	75	31
Male	51	108	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

<b>Reporting group values</b>	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	145		
Male	218		
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 received regorafenib 160 mg orally once daily 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 received 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 received atezolizumab monotherapy 1200 milligrams (mg) intravenous (IV) on Day 1 in a 21-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.	

### 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
Statistical analysis description: Stratification factors included extended RAS mutation status and time since diagnosis of first metastasis.	
Comparison groups	Regorafenib v Cobimetinib + Atezolizumab



Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
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

Notes:

[1] - Hazard ratio was estimated using stratified Cox regression.

<b>Statistical analysis title</b>	Atezolizumab vs. Regorafenib
Statistical analysis description:	
Stratification factors included extended RAS mutation status and time since diagnosis of first metastasis.	
Comparison groups	Regorafenib v Atezolizumab
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
P-value	= 0.336
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.71

Notes:

[2] - Hazard ratio was estimated using stratified Cox regression.

<b>Statistical analysis title</b>	Cobimetinib + Atezolizumab vs. Regorafenib
Comparison groups	Regorafenib v Cobimetinib + Atezolizumab
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
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

Notes:

[3] - Hazard ratio was estimated using unstratified Cox regression.

<b>Statistical analysis title</b>	Atezolizumab vs. Regorafenib
Comparison groups	Regorafenib v Atezolizumab
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority <sup>[4]</sup>
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

Notes:

[4] - Hazard ratio was estimated using unstratified Cox regression.

### **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)
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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
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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)

<b>End point values</b>	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
Statistical analysis description:	
Stratification factors included extended RAS mutation status and time since diagnosis of first metastasis.	
Comparison groups	Regorafenib v Cobimetinib + Atezolizumab
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority <sup>[5]</sup>
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

Notes:

[5] - Hazard ratio was estimated using stratified Cox regression.

Statistical analysis title	Atezolizumab vs. Regorafenib
Statistical analysis description:	
Stratification factors included extended RAS mutation status and time since diagnosis of first metastasis.	
Comparison groups	Regorafenib v Atezolizumab
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority <sup>[6]</sup>
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

Notes:

[6] - Hazard ratio was estimated using stratified Cox regression.

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 <sup>[7]</sup>
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

Notes:

[7] - Hazard ratio was estimated using stratified Cox regression.

<b>Statistical analysis title</b>	Atezolizumab vs. Regorafenib
Comparison groups	Regorafenib v Atezolizumab
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority <sup>[8]</sup>
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

Notes:

[8] - Hazard ratio was estimated using stratified Cox regression.

### **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
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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
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End point timeframe:

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

<b>End point values</b>	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

<b>Statistical analysis title</b>	Cobimetinib + Atezolizumab vs. Regorafenib
Statistical analysis description:	
Stratification factors included extended RAS mutation status and time since diagnosis of first metastasis.	
Comparison groups	Regorafenib v Cobimetinib + Atezolizumab
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority <sup>[9]</sup>
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

Notes:

[9] - 95% CI for difference in response rates was constructed using Hauck-Anderson method.

<b>Statistical analysis title</b>	Atezolizumab vs. Regorafenib
Statistical analysis description:	
Stratification factors included extended RAS mutation status and time since diagnosis of first metastasis.	
Comparison groups	Regorafenib v Atezolizumab
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority <sup>[10]</sup>
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

Notes:

[10] - 95% CI for difference in response rates was constructed using Hauck-Anderson method.

## 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
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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. Here 9999 = Value not available.

End point type	Secondary
End point timeframe:	
Baseline, end of the study (up to approximately 2.5 years)	

End point values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	125	61	
Units: units of a scale				
arithmetic mean (standard deviation)				
Week 3	9999 (± 9999)	9999 (± 9999)	-1.50 (± 10.56)	
Week 4	-6.52 (± 13.90)	-3.92 (± 11.05)	9999 (± 9999)	

Week 6	9999 (± 9999)	9999 (± 9999)	-0.14 (± 12.49)	
Week 8	-8.97 (± 13.95)	-3.23 (± 16.15)	9999 (± 9999)	
Week 9	9999 (± 9999)	9999 (± 9999)	-6.67 (± 17.19)	
Week 12	-7.78 (± 13.57)	-5.10 (± 15.54)	-6.40 (± 16.61)	
Week 15	9999 (± 9999)	9999 (± 9999)	-7.08 (± 14.90)	
Week 16	-9.12 (± 17.10)	-5.11 (± 16.67)	9999 (± 9999)	
Week 18	9999 (± 9999)	9999 (± 9999)	-3.70 (± 14.95)	
Week 20	-7.92 (± 19.51)	-0.87 (± 14.95)	9999 (± 9999)	
Week 21	9999 (± 9999)	9999 (± 9999)	-8.33 (± 17.37)	
Week 24	-5.45 (± 9.81)	-3.00 (± 18.67)	9999 (± 9999)	
Week 27	9999 (± 9999)	9999 (± 9999)	0.95 (± 15.60)	
Week 28	-5.00 (± 9.92)	-3.16 (± 15.29)	9999 (± 9999)	
Week 30	9999 (± 9999)	9999 (± 9999)	-8.00 (± 20.76)	
Week 32	-4.67 (± 11.35)	-10.74 (± 21.10)	9999 (± 9999)	
Week 33	9999 (± 9999)	9999 (± 9999)	-1.67 (± 13.74)	
Week 36	-12.22 (± 14.25)	-1.78 (± 16.23)	4.44 (± 15.40)	
Week 39	9999 (± 9999)	9999 (± 9999)	2.22 (± 19.25)	
Week 40	-5.00 (± 11.39)	-0.61 (± 16.18)	9999 (± 9999)	
Week 42	9999 (± 9999)	9999 (± 9999)	4.44 (± 15.40)	
Week 44	1.67 (± 3.33)	3.33 (± 16.07)	9999 (± 9999)	
Week 45	9999 (± 9999)	9999 (± 9999)	4.44 (± 15.40)	
Week 48	-13.33 (± 6.67)	1.82 (± 9.47)	0 (± 18.86)	
Week 51	9999 (± 9999)	9999 (± 9999)	0 (± 18.86)	
Week 52	-5.00 (± 6.38)	3.64 (± 10.05)	9999 (± 9999)	
Week 54	9999 (± 9999)	9999 (± 9999)	0 (± 18.86)	
Week 56	-2.22 (± 3.85)	5.00 (± 13.69)	9999 (± 9999)	
Week 57	9999 (± 9999)	9999 (± 9999)	0 (± 18.86)	
Week 60	-3.33 (± 4.71)	2.96 (± 11.60)	0 (± 18.86)	
Week 64	-6.67 (± 18.86)	-2.67 (± 10.11)	9999 (± 9999)	
Week 68	9999 (± 9999)	0 (± 0)	9999 (± 9999)	
Treatment Discontinuation	-17.00 (± 19.21)	-16.24 (± 23.49)	-11.79 (± 19.01)	
Long Term Follow Up Month 3	-22.29 (± 24.29)	-15.11 (± 16.80)	-20.00 (± 26.67)	
Long Term Follow Up Month 6	-14.07 (± 17.14)	-10.00 (± 14.14)	-8.00 (± 15.92)	
Long Term Follow Up Month 30	9999 (± 9999)	-20.00 (± 9999)	13.33 (± 9999)	
Long Term Follow Up Month 33	9999 (± 9999)	-20.00 (± 9999)	13.33 (± 9999)	
Long Term Follow Up Month 36	9999 (± 9999)	-20.00 (± 9999)	13.33 (± 9999)	

## 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
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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. Here 9999 = Value not available.

End point type	Secondary
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End point timeframe:

Baseline, end of the study (up to approximately 2.5 years)

End point values	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	125	57	
Units: units of a scale				
arithmetic mean (standard deviation)				
Week 3	-1.70 (± 17.76)	9999 (± 9999)	9999 (± 9999)	
Week 4	9999 (± 9999)	-7.00 (± 21.24)	-6.44 (± 18.84)	
Week 6	-4.86 (± 17.43)	9999 (± 9999)	9999 (± 9999)	
Week 8	9999 (± 9999)	-4.38 (± 22.58)	-8.05 (± 15.98)	
Week 9	-4.84 (± 15.78)	9999 (± 9999)	9999 (± 9999)	
Week 12	-3.67 (± 15.42)	-4.25 (± 18.51)	-1.04 (± 18.60)	
Week 15	-4.69 (± 12.16)	9999 (± 9999)	9999 (± 9999)	
Week 16	9999 (± 9999)	-1.94 (± 23.64)	-4.39 (± 18.08)	
Week 18	7.41 (± 12.16)	9999 (± 9999)	9999 (± 9999)	
Week 20	9999 (± 9999)	4.71 (± 23.28)	0.52 (± 18.38)	
Week 21	6.25 (± 19.29)	9999 (± 9999)	9999 (± 9999)	



Week 24	-6.94 (± 19.31)	3.75 (± 23.95)	-3.79 (± 20.19)	
Week 27	-2.38 (± 19.07)	9999 (± 9999)	9999 (± 9999)	
Week 28	9999 (± 9999)	0 (± 31.18)	-8.33 (± 17.25)	
Week 30	5.00 (± 15.14)	9999 (± 9999)	9999 (± 9999)	
Week 32	9999 (± 9999)	1.39 (± 23.79)	-5.00 (± 14.80)	
Week 33	6.25 (± 17.18)	9999 (± 9999)	9999 (± 9999)	
Week 36	16.67 (± 25.00)	5.56 (± 16.86)	0 (± 7.45)	
Week 39	22.22 (± 17.35)	9999 (± 9999)	9999 (± 9999)	
Week 40	9999 (± 9999)	11.36 (± 12.51)	2.08 (± 10.49)	
Week 42	25.00 (± 16.67)	9999 (± 9999)	9999 (± 9999)	
Week 44	9999 (± 9999)	9.52 (± 15.63)	0 (± 13.61)	
Week 45	19.44 (± 9.62)	9999 (± 9999)	9999 (± 9999)	
Week 48	8.33 (± 0)	10.61 (± 15.85)	-2.78 (± 4.81)	
Week 51	8.33 (± 0)	9999 (± 9999)	9999 (± 9999)	
Week 52	9999 (± 9999)	12.12 (± 17.62)	4.17 (± 15.96)	
Week 54	12.50 (± 5.89)	9999 (± 9999)	9999 (± 9999)	
Week 56	9999 (± 9999)	18.75 (± 9.71)	-5.56 (± 9.62)	
Week 57	8.33 (± 0)	9999 (± 9999)	9999 (± 9999)	
Week 60	8.33 (± 0)	16.67 (± 15.59)	-4.17 (± 17.68)	
Week 64	9999 (± 9999)	6.67 (± 24.58)	-4.17 (± 5.89)	
Week 68	9999 (± 9999)	0 (± 9999)	9999 (± 9999)	
Treatment Discontinuation	-14.53 (± 20.48)	-14.27 (± 25.98)	-19.87 (± 23.93)	
Long Term Follow-up Month 3	-11.36 (± 20.16)	-6.11 (± 22.15)	-21.30 (± 28.60)	
Long Term Follow-up Month 6	-11.67 (± 15.14)	-15.83 (± 15.44)	-13.89 (± 19.09)	
Long Term Follow-up Month 30	8.33 (± 9999)	0 (± 9999)	9999 (± 9999)	
Long Term Follow-up Month 33	8.33 (± 9999)	0 (± 9999)	9999 (± 9999)	
Long Term Follow-up Month 36	8.33 (± 9999)	0 (± 9999)	9999 (± 9999)	

## 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)
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, end of the study (up to approximately 2.5 years)

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)				
Serious Adverse Events	23.8	39.7	16.7	
Non-serious Adverse Events	97.5	97.8	93.3	

## 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 <sup>[11]</sup>	124	0 <sup>[12]</sup>	
Units: Nanogram/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 15 - Predose	()	195 (± 190.0)	()	
Cycle 1 Day 15 - Postdose	()	362 (± 89.4)	()	
Cycle 4 Day 15 - Predose	()	94.3 (± 741.9)	()	
Cycle 4 Day 15 - Postdose	()	210 (± 273.4)	()	

Notes:

[11] - Analysis only included participants to whom Cobimetinib was administered

[12] - Analysis only included participants to whom Cobimetinib was administered

## 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 2.5 years) (1 cycle = 28 days). Here 9999 = Value not available.

End point type	Secondary
End point timeframe:	
Pre-infusion (0 hours) on Day 1 of Cycle 1 up to approximately 2.5 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 <sup>[13]</sup>	179	89	
Units: microgram/milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 - Predose	()	9999 (± 9999)	9999 (± 9999)	
Cycle 1 Day 1 - 30 min post dose	()	259 (± 141.0)	348 (± 150.0)	
Cycle 2 Day 1 - Predose	()	68.2 (± 191.2)	81.5 (± 35.7)	
Cycle 2 Day 1 - 30 min post dose	()	9999 (± 9999)	56.2 (± 9999)	
Cycle 3 Day 1 - Predose	()	133 (± 51.2)	118 (± 48.4)	
Cycle 4 Day 1 - Predose	()	167 (± 48.4)	146 (± 52.4)	
Cycle 4 Day 1 - 30 min post dose	()	415 (± 37.2)	487 (± 41.5)	
Cycle 5 Day 1 - Predose	()	9999 (± 9999)	155 (± 9999)	
Cycle 5 Day 1 - 30 min post dose	()	9999 (± 9999)	456 (± 9999)	
Cycle 8 Day 1 - Predose	()	198 (± 52.6)	138 (± 54.6)	
Cycle 16 Day 1 - Predose	()	264 (± 9999)	226 (± 24.4)	
Treatment Discontinuation	()	76.6 (± 184.9)	97.9 (± 114.5)	
Unscheduled	()	0.539 (± 9999)	0.784 (± 2159.5)	

Notes:

[13] - Analysis only included participants to whom Atezolizumab was administered.

## 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
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End point description:

End point type	Secondary
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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 2.5 years) (1 cycle = 28 days)

<b>End point values</b>	Regorafenib	Cobimetinib + Atezolizumab	Atezolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 <sup>[14]</sup>	160	80	
Units: percentage of participants				
number (not applicable)		43.8	41.3	

Notes:

[14] - Analysis only included participants to whom Atezolizumab was administered.

### Statistical analyses

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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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### Reporting groups

Reporting group title	Atezolizumab
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Reporting group description:

Participants received atezolizumab monotherapy 1200 milligrams (mg) intravenous (IV) on Day 1 in a 21-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
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Reporting group description:

Participants received 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	Regorafenib
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Reporting group description:

Participants received regorafenib 160 mg orally once daily 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.

Serious adverse events	Atezolizumab	Cobimetinib + Atezolizumab	Regorafenib
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 90 (16.67%)	71 / 179 (39.66%)	19 / 80 (23.75%)
number of deaths (all causes)	72	136	62
number of deaths resulting from adverse events	0	5	2
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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
PELVIC VENOUS THROMBOSIS			
subjects affected / exposed	1 / 90 (1.11%)	0 / 179 (0.00%)	0 / 80 (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%)	12 / 179 (6.70%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	1 / 2	12 / 15	1 / 2
deaths causally related to treatment / all	1 / 2	12 / 15	1 / 2
ASTHENIA			
subjects affected / exposed	0 / 90 (0.00%)	0 / 179 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
CHILLS			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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
DEATH			
subjects affected / exposed	0 / 90 (0.00%)	0 / 179 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
FATIGUE			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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
INFLAMMATION			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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

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

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



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

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

subjects affected / exposed	0 / 90 (0.00%)	5 / 179 (2.79%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	2 / 5	0 / 0
Eye disorders			
MACULOPATHY			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	0 / 90 (0.00%)	6 / 179 (3.35%)	3 / 80 (3.75%)
occurrences causally related to treatment / all	0 / 0	6 / 6	3 / 3
deaths causally related to treatment / all	0 / 0	6 / 6	3 / 3
ABDOMINAL PAIN			
subjects affected / exposed	1 / 90 (1.11%)	2 / 179 (1.12%)	2 / 80 (2.50%)
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%)	2 / 179 (1.12%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	2 / 2	0 / 0
INTESTINAL PERFORATION			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	2 / 2
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	1 / 80 (1.25%)
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 / 179 (0.56%)	1 / 80 (1.25%)
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%)	0 / 179 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COLONIC FISTULA			
subjects affected / exposed	0 / 90 (0.00%)	0 / 179 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
CONSTIPATION			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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
ILEUS			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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
LOWER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 90 (0.00%)	0 / 179 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
NAUSEA			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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
PANCREATITIS			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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
RECTAL HAEMORRHAGE			
subjects affected / exposed	1 / 90 (1.11%)	0 / 179 (0.00%)	0 / 80 (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 / 179 (0.00%)	0 / 80 (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%)	1 / 179 (0.56%)	0 / 80 (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
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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
VOLVULUS OF SMALL BOWEL			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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
Hepatobiliary disorders			
AUTOIMMUNE HEPATITIS			
subjects affected / exposed	1 / 90 (1.11%)	0 / 179 (0.00%)	0 / 80 (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 / 179 (0.00%)	0 / 80 (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%)	1 / 179 (0.56%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	0 / 90 (0.00%)	1 / 179 (0.56%)	0 / 80 (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

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

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

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

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

<b>Non-serious adverse events</b>	Atezolizumab	Cobimetinib + Atezolizumab	Regorafenib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 90 (90.00%)	173 / 179 (96.65%)	78 / 80 (97.50%)
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	7 / 90 (7.78%)	8 / 179 (4.47%)	17 / 80 (21.25%)
occurrences (all)	7	9	18
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	6 / 90 (6.67%)	16 / 179 (8.94%)	7 / 80 (8.75%)
occurrences (all)	8	27	8
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 90 (0.00%)	22 / 179 (12.29%)	3 / 80 (3.75%)
occurrences (all)	0	39	5
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	8 / 90 (8.89%)	13 / 179 (7.26%)	1 / 80 (1.25%)
occurrences (all)	11	13	1
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	5 / 90 (5.56%)	10 / 179 (5.59%)	5 / 80 (6.25%)
occurrences (all)	5	17	6
LIPASE INCREASED			
subjects affected / exposed	1 / 90 (1.11%)	9 / 179 (5.03%)	6 / 80 (7.50%)
occurrences (all)	2	10	7
BLOOD THYROID STIMULATING HORMONE INCREASED			
subjects affected / exposed	3 / 90 (3.33%)	3 / 179 (1.68%)	4 / 80 (5.00%)
occurrences (all)	3	5	4
BLOOD BILIRUBIN INCREASED			

subjects affected / exposed	2 / 90 (2.22%)	3 / 179 (1.68%)	4 / 80 (5.00%)
occurrences (all)	2	3	7
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 90 (0.00%)	3 / 179 (1.68%)	5 / 80 (6.25%)
occurrences (all)	0	3	6
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	4 / 90 (4.44%)	9 / 179 (5.03%)	25 / 80 (31.25%)
occurrences (all)	6	10	31
Nervous system disorders			
HEADACHE			
subjects affected / exposed	11 / 90 (12.22%)	17 / 179 (9.50%)	10 / 80 (12.50%)
occurrences (all)	11	21	12
DIZZINESS			
subjects affected / exposed	0 / 90 (0.00%)	10 / 179 (5.59%)	3 / 80 (3.75%)
occurrences (all)	0	12	3
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	24 / 90 (26.67%)	65 / 179 (36.31%)	38 / 80 (47.50%)
occurrences (all)	28	75	46
PYREXIA			
subjects affected / exposed	12 / 90 (13.33%)	53 / 179 (29.61%)	20 / 80 (25.00%)
occurrences (all)	13	67	25
ASTHENIA			
subjects affected / exposed	12 / 90 (13.33%)	37 / 179 (20.67%)	17 / 80 (21.25%)
occurrences (all)	19	54	22
OEDEMA PERIPHERAL			
subjects affected / exposed	8 / 90 (8.89%)	27 / 179 (15.08%)	3 / 80 (3.75%)
occurrences (all)	9	32	3
MUCOSAL INFLAMMATION			
subjects affected / exposed	4 / 90 (4.44%)	16 / 179 (8.94%)	6 / 80 (7.50%)
occurrences (all)	6	19	8
CHILLS			
subjects affected / exposed	4 / 90 (4.44%)	14 / 179 (7.82%)	4 / 80 (5.00%)
occurrences (all)	5	15	4
FACE OEDEMA			

subjects affected / exposed occurrences (all)	0 / 90 (0.00%) 0	10 / 179 (5.59%) 12	0 / 80 (0.00%) 0
CHEST PAIN subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 2	5 / 179 (2.79%) 5	4 / 80 (5.00%) 4
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	5 / 90 (5.56%) 5	25 / 179 (13.97%) 28	8 / 80 (10.00%) 9
THROMBOCYTOPENIA subjects affected / exposed occurrences (all)	0 / 90 (0.00%) 0	10 / 179 (5.59%) 10	2 / 80 (2.50%) 2
Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences (all)	17 / 90 (18.89%) 23	115 / 179 (64.25%) 200	30 / 80 (37.50%) 58
NAUSEA subjects affected / exposed occurrences (all)	19 / 90 (21.11%) 23	67 / 179 (37.43%) 93	12 / 80 (15.00%) 13
VOMITING subjects affected / exposed occurrences (all)	13 / 90 (14.44%) 15	52 / 179 (29.05%) 79	9 / 80 (11.25%) 10
ABDOMINAL PAIN subjects affected / exposed occurrences (all)	13 / 90 (14.44%) 19	30 / 179 (16.76%) 34	21 / 80 (26.25%) 27
CONSTIPATION subjects affected / exposed occurrences (all)	11 / 90 (12.22%) 12	33 / 179 (18.44%) 41	17 / 80 (21.25%) 19
STOMATITIS subjects affected / exposed occurrences (all)	0 / 90 (0.00%) 0	18 / 179 (10.06%) 18	13 / 80 (16.25%) 21
DRY MOUTH subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 2	9 / 179 (5.03%) 9	4 / 80 (5.00%) 4
ABDOMINAL PAIN UPPER			

subjects affected / exposed occurrences (all)	7 / 90 (7.78%) 8	3 / 179 (1.68%) 3	2 / 80 (2.50%) 2
DYSPEPSIA subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 2	10 / 179 (5.59%) 10	0 / 80 (0.00%) 0
PROCTALGIA subjects affected / exposed occurrences (all)	0 / 90 (0.00%) 0	2 / 179 (1.12%) 2	4 / 80 (5.00%) 4
Respiratory, thoracic and mediastinal disorders DYSпноEA subjects affected / exposed occurrences (all)	12 / 90 (13.33%) 12	36 / 179 (20.11%) 41	13 / 80 (16.25%) 13
COUGH subjects affected / exposed occurrences (all)	12 / 90 (13.33%) 12	33 / 179 (18.44%) 35	8 / 80 (10.00%) 10
DYSPHONIA subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1	0 / 179 (0.00%) 0	19 / 80 (23.75%) 27
EPISTAXIS subjects affected / exposed occurrences (all)	0 / 90 (0.00%) 0	9 / 179 (5.03%) 9	7 / 80 (8.75%) 7
OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 2	7 / 179 (3.91%) 8	5 / 80 (6.25%) 6
Skin and subcutaneous tissue disorders RASH subjects affected / exposed occurrences (all)	8 / 90 (8.89%) 8	85 / 179 (47.49%) 122	17 / 80 (21.25%) 19
DERMATITIS ACNEIFORM subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 3	46 / 179 (25.70%) 56	2 / 80 (2.50%) 2
PALMAR–PLANTAR ERYTHRODYSAESTHESIA SYNDROME subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1	3 / 179 (1.68%) 3	42 / 80 (52.50%) 69
PRURITUS			

subjects affected / exposed occurrences (all)	3 / 90 (3.33%) 3	22 / 179 (12.29%) 25	2 / 80 (2.50%) 2
DRY SKIN subjects affected / exposed occurrences (all)	3 / 90 (3.33%) 3	14 / 179 (7.82%) 14	1 / 80 (1.25%) 1
RASH MACULO–PAPULAR subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1	11 / 179 (6.15%) 12	3 / 80 (3.75%) 3
ERYTHEMA subjects affected / exposed occurrences (all)	0 / 90 (0.00%) 0	2 / 179 (1.12%) 3	5 / 80 (6.25%) 5
Psychiatric disorders INSOMNIA subjects affected / exposed occurrences (all)	6 / 90 (6.67%) 6	9 / 179 (5.03%) 9	3 / 80 (3.75%) 3
Musculoskeletal and connective tissue disorders BACK PAIN subjects affected / exposed occurrences (all)	13 / 90 (14.44%) 15	11 / 179 (6.15%) 11	8 / 80 (10.00%) 10
ARTHRALGIA subjects affected / exposed occurrences (all)	8 / 90 (8.89%) 8	14 / 179 (7.82%) 14	5 / 80 (6.25%) 6
PAIN IN EXTREMITY subjects affected / exposed occurrences (all)	6 / 90 (6.67%) 6	12 / 179 (6.70%) 16	6 / 80 (7.50%) 7
MYALGIA subjects affected / exposed occurrences (all)	3 / 90 (3.33%) 3	9 / 179 (5.03%) 12	7 / 80 (8.75%) 10
MUSCULOSKELETAL PAIN subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 2	5 / 179 (2.79%) 5	4 / 80 (5.00%) 4
MUSCLE SPASMS subjects affected / exposed occurrences (all)	0 / 90 (0.00%) 0	3 / 179 (1.68%) 3	6 / 80 (7.50%) 6
Infections and infestations			

URINARY TRACT INFECTION subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 2	8 / 179 (4.47%) 10	4 / 80 (5.00%) 8
UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	6 / 90 (6.67%) 6	4 / 179 (2.23%) 6	3 / 80 (3.75%) 4
Metabolism and nutrition disorders			
DECREASED APPETITE subjects affected / exposed occurrences (all)	21 / 90 (23.33%) 27	48 / 179 (26.82%) 54	33 / 80 (41.25%) 39
HYPOPHOSPHATAEMIA subjects affected / exposed occurrences (all)	3 / 90 (3.33%) 3	11 / 179 (6.15%) 11	7 / 80 (8.75%) 7
HYPOKALAEMIA subjects affected / exposed occurrences (all)	1 / 90 (1.11%) 1	14 / 179 (7.82%) 17	3 / 80 (3.75%) 4
HYPOCALCAEMIA subjects affected / exposed occurrences (all)	2 / 90 (2.22%) 2	7 / 179 (3.91%) 7	5 / 80 (6.25%) 5

## 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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported