



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

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

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

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 6 / 90 (6.67%) 6 | 2 / 80 (2.50%) 2 | 4 / 179 (2.23%) 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: