



Clinical trial results:

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

Summary

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

Results information

| | |
|--------------------------------|--------------|
| Result version number | v2 |
| This version publication date | 02 July 2023 |
| First version publication date | 21 July 2022 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | MO39136 |
|-----------------------|---------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 07 June 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 June 2021 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |

| | |
|----------------------|----|
| Adults (18-64 years) | 56 |
| From 65 to 84 years | 24 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 22 centers in 7 countries.

Pre-assignment

Screening details:

A total of 80 participants were enrolled at 22 centers.

Period 1

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

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--|
| Arm title | Cohort 1- cobimetinib and atezolizumab |
|------------------|--|

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

| | |
|------------------|--|
| Arm title | Cohort 2 - cobimetinib, atezolizumab and vemurafenib |
|------------------|--|

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

| Number of subjects in period 1 | Cohort 1- cobimetinib and atezolizumab | Cohort 2 - cobimetinib, atezolizumab and vemurafenib |
|--------------------------------|--|---|
| | | |
| Started | 15 | 65 |
| Completed | 0 | 0 |
| Not completed | 15 | 65 |
| Consent withdrawn by subject | 1 | - |
| Death | 11 | 37 |
| Withdrawal of Consent | - | 1 |
| Continuing in study | 3 | 27 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Cohort 1- cobimetinib and atezolizumab |
|-----------------------|--|

Reporting group description:

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

| | |
|-----------------------|--|
| Reporting group title | Cohort 2 - cobimetinib, atezolizumab and vemurafenib |
|-----------------------|--|

Reporting group description:

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

| Reporting group values | Cohort 1- cobimetinib and atezolizumab | Cohort 2 - cobimetinib, atezolizumab and vemurafenib | Total |
|---|--|---|-------|
| Number of subjects | 15 | 65 | 80 |
| Age Categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 8 | 48 | 56 |
| From 65-84 years | 7 | 17 | 24 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 60.9 | 54.4 | - |
| standard deviation | ± 12.5 | ± 13.8 | |
| Gender Categorical Units: Subjects | | | |
| Female | 9 | 24 | 33 |
| Male | 6 | 41 | 47 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 0 | 9 | 9 |
| Not Hispanic or Latino | 11 | 50 | 61 |
| Not Stated | 0 | 5 | 5 |
| Unknown | 4 | 1 | 5 |
| Race (NIH/OMB) Units: Subjects | | | |
| White | 11 | 61 | 72 |
| Unknown | 4 | 4 | 8 |

End points

End points reporting groups

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

Primary: Intracranial Objective Response Rate (ORR)

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

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

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|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

Notes:

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

Justification: No statistical analyses were performed for this endpoint

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

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

| | |
|-----------------|---------------------------------|
| End point title | Progression-Free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

| End point values | Cohort 1- cobimetinib and atezolizumab | Cohort 2 - cobimetinib, atezolizumab and vemurafenib | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 65 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Intracranial (n=12,48) | 2.17 (1.74 to 7.98) | 5.59 (5.36 to 7.39) | | |

| | | | | |
|------------------------|----------------------|----------------------|--|--|
| Extracranial (n=11,39) | 4.21 (1.84 to 12.65) | 9.43 (6.90 to 13.67) | | |
| Overall (n=12,49) | 1.81 (1.71 to 3.71) | 5.49 (5.13 to 7.43) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall ORR

| | |
|-----------------|-------------|
| End point title | Overall ORR |
|-----------------|-------------|

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

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

Statistical analyses

No statistical analyses for this end point

Secondary: Extracranial ORR

| | |
|-----------------|------------------|
| End point title | Extracranial ORR |
|-----------------|------------------|

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

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

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 16 weeks

Notes:

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

| End point values | Cohort 2 - cobimetinib, atezolizumab and vemurafenib | | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 65 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Intracranial (n=25) | 38.5 (26.85 to 51.36) | | | |

| | | | | |
|---------------------|-----------------------|--|--|--|
| Extracranial (n=33) | 50.8 (38.07 to 63.40) | | | |
| Overall (n=33) | 50.8 (38.07 to 63.40) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

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

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

Notes:

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

| End point values | Cohort 2 - cobimetinib, atezolizumab and vemurafenib | | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 65 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Intracranial (n=32) | 5.72 (5.52 to 10.15) | | | |
| Extracranial (n=37) | 11.89 (7.89 to 18.10) | | | |
| Overall (n=34) | 7.36 (5.52 to 9.92) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|-----------------|--------------------------------------|
| End point title | Overall Survival (OS) ^[4] |
|-----------------|--------------------------------------|

End point description:

OS is defined as the time from study treatment initiation to death from any cause. Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to approximately 4 years

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

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

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Cohort 2 - cobimetinib, atezolizumab and vemurafenib | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[5] | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | | | |

Notes:

[5] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptom and Function Deterioration

| | |
|-----------------|--|
| End point title | Time to Symptom and Function Deterioration |
|-----------------|--|

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 48 months

| | | | | |
|----------------------------------|------------------------------------|------------------------------------|--|--|
| End point values | PRO-evaluable Population: Cohort 1 | PRO-evaluable Population: Cohort 2 | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 63 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Physical Functioning | 9999999 (0.99 to 9999999) | 9999999 (5.55 to 9999999) | | |

| | | | | |
|-----------------------|-------------------------|------------------------|--|--|
| Cognitive Functioning | 11.99 (1.91 to 9999999) | 8.25 (5.55 to 9999999) | | |
| Role Functioning | 2.83 (1.35 to 6.47) | 4.07 (1.61 to 6.47) | | |
| Fatigue | 1.35 (0.95 to 9999999) | 1.45 (1.38 to 6.47) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cognitive Symptom Deterioration

| | |
|-----------------|---|
| End point title | Time to Cognitive Symptom Deterioration |
|-----------------|---|

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 48 months

| End point values | PRO-evaluable Population: Cohort 1 | PRO-evaluable Population: Cohort 2 | | |
|----------------------------------|------------------------------------|------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 63 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Visual Disorder | 3.75 (1.87 to 9999999) | 2.99 (1.41 to 8.74) | | |
| Motor Dysfunction | 1.87 (1.08 to 19.84) | 6.70 (3.94 to 16.62) | | |
| Communication Deficit | 6.44 (2.83 to 9999999) | 9999999 (6.54 to 9999999) | | |
| Headaches | 9999999 (1.08 to 9999999) | 10.84 (5.55 to 9999999) | | |
| Seizures | 8.31 (8.31 to 9999999) | 9999999 (9999999 to 9999999) | | |
| Drowsiness | 2.83 (1.08 to 9999999) | 7.16 (1.94 to 9999999) | | |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

| End point values | PRO-evaluable Population: Cohort 1 | PRO-evaluable Population: Cohort 2 | | |
|----------------------------------|------------------------------------|------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 63 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (15.21 to 9999999) | 5.98 (3.68 to 10.32) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events

| | |
|-----------------|--|
| End point title | Percentage of Participants with Adverse Events |
|-----------------|--|

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to cut of date (approximately 2.5 years)

| End point values | Safety-evaluable Population: Cohort 1 | Safety-evaluable Population: Cohort 2 | Safety-evaluable Population: Cohort 2 (no atezolizumab) | |
|-----------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 15 | 60 | 5 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Occurrence (n=15,60,5) | 100 | 100 | 100 | |
| Grade 1 (n=1,3,0) | 6.7 | 5.0 | 0 | |
| Grade 2 (n=4,13,1) | 26.7 | 21.7 | 20.0 | |
| Grade 3 (n=8,36,2) | 53.3 | 60.0 | 40.0 | |
| Grade 4 (n=1,8,0) | 6.7 | 13.3 | 0 | |
| Grade 5 (n=1,0,2) | 6.7 | 0 | 40.0 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to cut of date (approximately 2.5 years)

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Cohort 1- cobimetinib and atezolizumab |
|-----------------------|--|

Reporting group description:

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

| | |
|-----------------------|--|
| Reporting group title | Cohort 2 - cobimetinib and vemurafenib |
|-----------------------|--|

Reporting group description:

There were 5 participants in Cohort 2 administered with cobimetinib and vemurafenib only as they dropped out during the run-in period.

| | |
|-----------------------|--|
| Reporting group title | Cohort 2 - cobimetinib, atezolizumab and vemurafenib |
|-----------------------|--|

Reporting group description:

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

| Serious adverse events | Cohort 1- cobimetinib and atezolizumab | Cohort 2 - cobimetinib and vemurafenib | Cohort 2 - cobimetinib, atezolizumab and vemurafenib |
|---|--|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 15 (33.33%) | 5 / 5 (100.00%) | 19 / 60 (31.67%) |
| number of deaths (all causes) | 11 | 2 | 35 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Oedema | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|---------------|----------------|
| Death | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac failure | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limbic encephalitis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gallbladder rupture | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 5 (20.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 5 (20.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pustular psoriasis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug reaction with eosinophilia and systemic symptoms | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 5 (20.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 5 (20.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash morbilliform | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myositis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------------------------|----------------------------------|----------------------------------|
| Infections and infestations Diverticulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 15 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 2 / 60 (3.33%) 1 / 2 0 / 0 |
| Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 15 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 1 / 60 (1.67%) 0 / 1 0 / 0 |
| Postoperative wound infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 15 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 1 / 60 (1.67%) 0 / 1 0 / 0 |
| Bacterial diarrhoea subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 15 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 1 / 60 (1.67%) 0 / 1 0 / 0 |
| Septic shock subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 15 (0.00%) 0 / 0 0 / 0 | 1 / 5 (20.00%) 0 / 1 0 / 1 | 0 / 60 (0.00%) 0 / 0 0 / 0 |
| Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 15 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 1 / 60 (1.67%) 0 / 1 0 / 0 |
| Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 15 (0.00%) 0 / 0 0 / 0 | 0 / 5 (0.00%) 0 / 0 0 / 0 | 1 / 60 (1.67%) 0 / 1 0 / 0 |

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

| Non-serious adverse events | Cohort 1- cobimetinib and atezolizumab | Cohort 2 - cobimetinib and vemurafenib | Cohort 2 - cobimetinib, atezolizumab and vemurafenib |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 15 (100.00%) | 4 / 5 (80.00%) | 60 / 60 (100.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 0 / 5 (0.00%) | 10 / 60 (16.67%) |
| occurrences (all) | 2 | 0 | 12 |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 2 / 60 (3.33%) |
| occurrences (all) | 1 | 0 | 3 |
| Mass | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | 0 / 5 (0.00%) | 17 / 60 (28.33%) |
| occurrences (all) | 4 | 0 | 21 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 6 / 60 (10.00%) |
| occurrences (all) | 1 | 0 | 12 |
| Malaise | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | 1 / 5 (20.00%) | 26 / 60 (43.33%) |
| occurrences (all) | 5 | 1 | 51 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 7 / 60 (11.67%) |
| occurrences (all) | 2 | 0 | 8 |

| | | | |
|---|----------------------|---------------------|---------------------|
| Fatigue subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 4 / 60 (6.67%) 4 |
| Xerosis subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 60 (0.00%) 0 |
| Immune system disorders Contrast media allergy subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 4 / 60 (6.67%) 4 |
| Pneumonitis subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 5 / 60 (8.33%) 5 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 1 / 60 (1.67%) 1 |
| Cough subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 2 | 0 / 5 (0.00%) 0 | 4 / 60 (6.67%) 4 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 5 (0.00%) 0 | 5 / 60 (8.33%) 6 |
| Confusional state subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 5 (0.00%) 0 | 3 / 60 (5.00%) 3 |
| Investigations Blood magnesium decreased | | | |

| | | | |
|--|-----------------|---------------|------------------|
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 0 | 4 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 10 / 60 (16.67%) |
| occurrences (all) | 0 | 0 | 10 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 0 / 5 (0.00%) | 13 / 60 (21.67%) |
| occurrences (all) | 2 | 0 | 17 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 18 / 60 (30.00%) |
| occurrences (all) | 0 | 0 | 24 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 9 / 60 (15.00%) |
| occurrences (all) | 0 | 0 | 12 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 0 / 5 (0.00%) | 25 / 60 (41.67%) |
| occurrences (all) | 16 | 0 | 59 |
| Thyroxine free increased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 4 / 60 (6.67%) |
| occurrences (all) | 0 | 0 | 4 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 23 / 60 (38.33%) |
| occurrences (all) | 0 | 0 | 42 |
| Blood cholesterol increased | | | |

| | | | |
|---|---------------------|--------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 5 (0.00%) 0 | 3 / 60 (5.00%) 4 |
| Tri-iodothyronine free decreased subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 12 / 60 (20.00%) 21 |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 4 / 60 (6.67%) 9 |
| Cardiac disorders Myocardial infarction subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Mitral valve incompetence subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Left ventricular dysfunction subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Nervous system disorders Sciatica subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Tremor subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 5 / 60 (8.33%) 5 |
| Headache subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 3 | 0 / 5 (0.00%) 0 | 6 / 60 (10.00%) 9 |
| Dizziness | | | |

| | | | |
|--|---------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 2 / 60 (3.33%) 2 |
| Blood and lymphatic system disorders | | | |
| Eosinophilia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 5 (20.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Anaemia | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | 1 / 5 (20.00%) | 9 / 60 (15.00%) |
| occurrences (all) | 4 | 1 | 9 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 5 (20.00%) | 2 / 60 (3.33%) |
| occurrences (all) | 0 | 1 | 2 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 5 / 60 (8.33%) |
| occurrences (all) | 0 | 0 | 5 |
| Keratitis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 5 (20.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Eye pain | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 5 (20.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Uveitis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 0 | 4 |
| Serous retinopathy | | | |

| | | | |
|--|-----------------|----------------|------------------|
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 8 / 60 (13.33%) |
| occurrences (all) | 0 | 0 | 8 |
| Detachment of retinal pigment epithelium | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 0 | 5 |
| Serous retinal detachment | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 1 | 0 | 3 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 4 / 60 (6.67%) |
| occurrences (all) | 1 | 0 | 4 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 6 / 60 (10.00%) |
| occurrences (all) | 0 | 0 | 6 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 5 (20.00%) | 4 / 60 (6.67%) |
| occurrences (all) | 1 | 1 | 4 |
| Nausea | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 0 / 5 (0.00%) | 14 / 60 (23.33%) |
| occurrences (all) | 2 | 0 | 22 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 2 / 60 (3.33%) |
| occurrences (all) | 1 | 0 | 2 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 0 | 4 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Stomatitis | | | |

| | | | |
|---|-----------------------|---------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 5 (0.00%) 0 | 5 / 60 (8.33%) 5 |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 4 | 1 / 5 (20.00%) 1 | 10 / 60 (16.67%) 15 |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 7 / 60 (11.67%) 7 |
| Diarrhoea subjects affected / exposed occurrences (all) | 6 / 15 (40.00%) 15 | 0 / 5 (0.00%) 0 | 29 / 60 (48.33%) 53 |
| Mouth ulceration subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 60 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 6 / 60 (10.00%) 7 |
| Hepatobiliary disorders Hepatic cytolysis subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 1 / 5 (20.00%) 1 | 0 / 60 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Photosensitivity reaction subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 5 (0.00%) 0 | 10 / 60 (16.67%) 14 |
| Rash follicular subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 1 / 60 (1.67%) 1 |
| Alopecia subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 5 (0.00%) 0 | 5 / 60 (8.33%) 5 |
| Vitiligo subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 5 (0.00%) 0 | 3 / 60 (5.00%) 3 |
| Rash | | | |

| | | | |
|-----------------------------|-----------------|----------------|------------------|
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 20 / 60 (33.33%) |
| occurrences (all) | 1 | 0 | 29 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 1 / 5 (20.00%) | 17 / 60 (28.33%) |
| occurrences (all) | 2 | 1 | 20 |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 2 / 60 (3.33%) |
| occurrences (all) | 1 | 0 | 2 |
| Erythema | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 1 | 0 | 5 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 1 / 5 (20.00%) | 9 / 60 (15.00%) |
| occurrences (all) | 2 | 1 | 9 |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 4 / 60 (6.67%) |
| occurrences (all) | 0 | 0 | 5 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 4 / 15 (26.67%) | 0 / 5 (0.00%) | 16 / 60 (26.67%) |
| occurrences (all) | 8 | 0 | 20 |
| Scab | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypothyroidism | | | |

| | | | |
|---|----------------------|---------------------|------------------------|
| subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 8 / 60 (13.33%) 8 |
| Musculoskeletal and connective tissue disorders | | | |
| Sjogren's syndrome subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 5 (0.00%) 0 | 5 / 60 (8.33%) 5 |
| Myalgia subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 5 (0.00%) 0 | 10 / 60 (16.67%) 14 |
| Arthralgia subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 2 | 1 / 5 (20.00%) 1 | 17 / 60 (28.33%) 22 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 5 (0.00%) 0 | 4 / 60 (6.67%) 4 |
| Infections and infestations | | | |
| COVID-19 subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 2 / 60 (3.33%) 2 |
| Fungal skin infection subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Hordeolum subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 60 (0.00%) 0 |
| Rash pustular subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 2 | 0 / 5 (0.00%) 0 | 2 / 60 (3.33%) 3 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 5 (0.00%) 0 | 1 / 60 (1.67%) 1 |
| Rhinitis | | | |

| | | | |
|------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Furuncle | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 4 / 60 (6.67%) |
| occurrences (all) | 0 | 0 | 4 |
| Metabolism and nutrition disorders | | | |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 2 / 60 (3.33%) |
| occurrences (all) | 1 | 0 | 2 |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 4 / 60 (6.67%) |
| occurrences (all) | 1 | 0 | 4 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 3 / 60 (5.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 5 (20.00%) | 7 / 60 (11.67%) |
| occurrences (all) | 1 | 1 | 10 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 5 / 60 (8.33%) |
| occurrences (all) | 0 | 0 | 5 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Cell death | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 5 (20.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 5 (0.00%) | 5 / 60 (8.33%) |
| occurrences (all) | 0 | 0 | 5 |
| Iron deficiency | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 5 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: