



Clinical trial results:

A Phase III, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study of Atezolizumab (AntiPD-L1 Antibody) as Adjuvant Therapy in Patients With Renal Cell Carcinoma at High Risk of Developing Metastasis Following Nephrectomy

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2016-001881-27 |
| Trial protocol | AT NL DE GB DK CZ BE PL ES IE FR IT |
| Global end of trial date | 08 December 2022 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v3 (current) |
| This version publication date | 30 July 2023 |
| First version publication date | 04 May 2023 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | WO39210 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03024996 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 08 December 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 December 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the efficacy and safety of atezolizumab versus placebo in participants with renal cell carcinoma (RCC) who were at high risk of disease recurrence following resection.

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 | 03 January 2017 |
| 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 | Argentina: 8 |
| Country: Number of subjects enrolled | Australia: 14 |
| Country: Number of subjects enrolled | Austria: 8 |
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | Brazil: 36 |
| Country: Number of subjects enrolled | Canada: 43 |
| Country: Number of subjects enrolled | Chile: 13 |
| Country: Number of subjects enrolled | China: 5 |
| Country: Number of subjects enrolled | Czechia: 11 |
| Country: Number of subjects enrolled | Denmark: 30 |
| Country: Number of subjects enrolled | France: 22 |
| Country: Number of subjects enrolled | Germany: 13 |
| Country: Number of subjects enrolled | Ireland: 13 |
| Country: Number of subjects enrolled | Israel: 11 |
| Country: Number of subjects enrolled | Italy: 53 |
| Country: Number of subjects enrolled | Japan: 39 |
| Country: Number of subjects enrolled | Korea, Republic of: 17 |
| Country: Number of subjects enrolled | Netherlands: 13 |
| Country: Number of subjects enrolled | Poland: 23 |
| Country: Number of subjects enrolled | Russian Federation: 44 |
| Country: Number of subjects enrolled | Serbia: 8 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 36 |
| Country: Number of subjects enrolled | Taiwan: 16 |
| Country: Number of subjects enrolled | Thailand: 4 |
| Country: Number of subjects enrolled | Turkey: 8 |
| Country: Number of subjects enrolled | Ukraine: 30 |
| Country: Number of subjects enrolled | United Kingdom: 16 |
| Country: Number of subjects enrolled | United States: 239 |
| Worldwide total number of subjects | 778 |
| EEA total number of subjects | 227 |

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) | 496 |
| From 65 to 84 years | 282 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

5 participants were randomized but did not receive any treatment.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

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

| | |
|------------------|--------------|
| Arm title | Atezolizumab |
|------------------|--------------|

Arm description:

Participants received atezolizumab 1200 milligrams (mg) intravenous (IV) infusion every 3 weeks (q3w) for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first).

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

Dosage and administration details:

Participants received atezolizumab 1200 mg administered via IV q3w for 16 cycles or 1 year (whichever occurred first).

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Participants received placebo matching to atezolizumab q3w for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first).

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

Dosage and administration details:

Participants received a placebo administered via IV q3w for 16 cycles or 1 year (whichever occurred first).

| Number of subjects in period 1 | Atezolizumab | Placebo |
|---------------------------------------|--------------|---------|
| Started | 390 | 388 |
| Completed | 0 | 0 |
| Not completed | 390 | 388 |
| Consent withdrawn by subject | 21 | 36 |
| Physician decision | - | 1 |
| Death | 57 | 55 |
| Not specified | 3 | 3 |
| Disease relapse | 1 | - |
| Study terminated by sponsor | 303 | 283 |
| Lost to follow-up | 5 | 10 |

Baseline characteristics

Reporting groups

| | |
|--|--------------|
| Reporting group title | Atezolizumab |
| Reporting group description: | |
| Participants received atezolizumab 1200 milligrams (mg) intravenous (IV) infusion every 3 weeks (q3w) for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first). | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received placebo matching to atezolizumab q3w for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first) | |

| Reporting group values | Atezolizumab | Placebo | Total |
|--|--------------|---------|-------|
| Number of subjects | 390 | 388 | 778 |
| 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) | 248 | 248 | 496 |
| From 65-84 years | 142 | 140 | 282 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 59.7 | 59.6 | - |
| standard deviation | ± 11.3 | ± 10.7 | - |
| Gender Categorical | | | |
| Units: Participants | | | |
| Female | 103 | 110 | 213 |
| Male | 287 | 278 | 565 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 41 | 38 | 79 |
| Not Hispanic or Latino | 334 | 327 | 661 |
| Unknown or Not Reported | 15 | 23 | 38 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | 2 |
| Asian | 43 | 51 | 94 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 8 | 9 | 17 |
| White | 324 | 304 | 628 |
| More than one race | 0 | 1 | 1 |
| Unknown or Not Reported | 14 | 22 | 36 |

End points

End points reporting groups

| | |
|--|--------------|
| Reporting group title | Atezolizumab |
| Reporting group description: Participants received atezolizumab 1200 milligrams (mg) intravenous (IV) infusion every 3 weeks (q3w) for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first). | |
| Reporting group title | Placebo |
| Reporting group description: Participants received placebo matching to atezolizumab q3w for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first) | |

Primary: Investigator-assessed Disease-Free Survival (DFS)

| | |
|---|---|
| End point title | Investigator-assessed Disease-Free Survival (DFS) |
| End point description: Investigator-assessed DFS, defined as the time from randomization to death from any cause or the first documented recurrence assessed by investigator, whichever occurred first. Recurrence was defined as any of the following: Local recurrence of renal cell carcinoma (RCC), new primary RCC, or distant metastasis of RCC. Investigator-assessed DFS was analyzed similarly to the analysis of IRF-assessed DFS. The Intent-to-Treat (ITT) population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=small number of events to calculate the upper CI limit | |
| End point type | Primary |
| End point timeframe: From baseline up to first occurrence of event by investigator assessment (up to approximately 64 months) | |

| End point values | Atezolizumab | Placebo | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 390 | 388 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 57.2 (44.6 to 9999999) | 49.5 (47.4 to 9999999) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Investigator-Assessed DFS |
| Comparison groups | Atezolizumab v Placebo |
| Number of subjects included in analysis | 778 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.495 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.15 |

Secondary: Overall Survival (OS)

| | |
|---|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| OS was defined as the time from randomization to death from any cause. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=wasn't estimable due to small or no number of events. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline up to death due to any cause (up to approximately 64 months) | |

| End point values | Atezolizumab | Placebo | | |
|----------------------------------|---------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 390 | 388 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (59.8 to 9999999) | 9999999 (9999999 to 9999999) | | |

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | OS |
| Comparison groups | Atezolizumab v Placebo |
| Number of subjects included in analysis | 778 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8868 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.42 |

Secondary: Investigator-assessed DFS in Participants With Tumor-Infiltrating

Immune Cell (IC) 1/2/3

| | |
|-----------------|--|
| End point title | Investigator-assessed DFS in Participants With Tumor-Infiltrating Immune Cell (IC) 1/2/3 |
|-----------------|--|

End point description:

Investigator assessed DFS for participants with PD-L1 expression of IC1/2/3 vs IC0, defined as the time from randomization to death from any cause or the first documented recurrence assessed by investigator, whichever occurred first. Investigator-assessed DFS was analyzed similarly to the analysis of IRF-assessed DFS. PD-L1 IC0 was defined as <1% and IC1/2/3 was defined as ≥1% of tumor-infiltrating IC expressing PD-L1 as assessed by immunohistochemistry using SP142 assay. Recurrence was defined as any of the following: Local recurrence of renal cell carcinoma (RCC), new primary RCC, or distant metastasis of RCC. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=small number of events to calculate the upper CI limit

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

End point timeframe:

From baseline until first occurrence of DFS event (up to approximately 64 months)

| End point values | Atezolizumab | Placebo | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 390 | 388 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 57.2 (44.6 to 9999999) | 47.9 (38.6 to 9999999) | | |

Statistical analyses

| | |
|-----------------------------------|---------------------------|
| Statistical analysis title | Investigator-assessed DFS |
|-----------------------------------|---------------------------|

Statistical analysis description:

Participants With Tumor-Infiltrating IC 1/2/3

| | |
|---|------------------------|
| Comparison groups | Atezolizumab v Placebo |
| Number of subjects included in analysis | 778 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.201 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 1.1 |

Secondary: IRF-assessed Event-free Survival (EFS)

| | |
|-----------------|--|
| End point title | IRF-assessed Event-free Survival (EFS) |
|-----------------|--|

End point description:

IRF-assessed EFS was defined as the time from randomization to death from any cause, or the first documented recurrence in participants without baseline disease by IRF or the first documented disease progression in participants identified as having baseline disease by IRF, whichever occurred first. Disease progression was defined as either unequivocal progression of baseline disease or new unequivocal lesions. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=wasn't estimable due to small number of events.

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

End point timeframe:

From baseline until first documented recurrence event (up to approximately 64 months)

| End point values | Atezolizumab | Placebo | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 390 | 388 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (54.1 to 9999999) | 9999999 (45.4 to 9999999) | | |

Statistical analyses

| Statistical analysis title | IRF-assessed EFS |
|---|------------------------|
| Comparison groups | Atezolizumab v Placebo |
| Number of subjects included in analysis | 778 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1396 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.06 |

Secondary: Independent Review Facility (IRF)-assessed DFS

| | |
|-----------------|--|
| End point title | Independent Review Facility (IRF)-assessed DFS |
|-----------------|--|

End point description:

IRF-assessed DFS was defined as the time from randomization to death from any cause or the first documented recurrence assessed by IRF, whichever occurred first. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=wasn't estimable due to small number of events.

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

End point timeframe:

From baseline until first documented recurrence event (up to approximately 64 months)

| End point values | Atezolizumab | Placebo | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 390 | 388 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (54.1 to 9999999) | 9999999 (49.4 to 9999999) | | |

Statistical analyses

| Statistical analysis title | IRF-assessed DFS |
|---|------------------------|
| Comparison groups | Atezolizumab v Placebo |
| Number of subjects included in analysis | 778 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2811 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.12 |

Secondary: IRF-assessed DFS in Participants With Tumor-Infiltrating IC 1/2/3

| | |
|-----------------|---|
| End point title | IRF-assessed DFS in Participants With Tumor-Infiltrating IC 1/2/3 |
|-----------------|---|

End point description:

IRF-assessed DFS was defined as the time from randomization to death from any cause or the first documented recurrence assessed by IRF, whichever occurred first. PD-L1 IC0 was defined as <1% and IC1/2/3 was defined as ≥1% of tumor-infiltrating IC expressing PD-L1 as assessed by immunohistochemistry using SP142 assay. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=wasn't estimable due to small or no number of events.

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

End point timeframe:

From baseline until first occurrence of DFS event (up to approximately 64 months)

| End point values | Atezolizumab | Placebo | | |
|----------------------------------|---------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 232 | 235 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (9999999 to 9999999) | 9999999 (41.4 to 9999999) | | |

Statistical analyses

| Statistical analysis title | IRF-assessed DFS (Tumor-Infiltrating IC 1/2/3) |
|---|--|
| Comparison groups | Atezolizumab v Placebo |
| Number of subjects included in analysis | 467 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0735 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 1.03 |

Secondary: Distant Metastasis-Free Survival

| | |
|------------------------|---|
| End point title | Distant Metastasis-Free Survival |
| End point description: | Distant metastasis-free survival, defined as the time from randomization to death from any cause or the date of diagnosis of distant (i.e., non-locoregional) metastases assessed by the investigator, whichever occurred first. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=wasn't estimable due to small number of events. |
| End point type | Secondary |
| End point timeframe: | From baseline up to date of diagnosis of distant metastases or death due to any cause (up to approximately 64 months) |

| End point values | Atezolizumab | Placebo | | |
|----------------------------------|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 390 | 388 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (48.4 to 9999999) | 52.9 (47.9 to 9999999) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Distant Metastasis-Free Survival |
| Comparison groups | Atezolizumab v Placebo |
| Number of subjects included in analysis | 778 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5111 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.16 |

Secondary: Disease-Specific Survival

| | |
|--|---------------------------|
| End point title | Disease-Specific Survival |
| End point description: | |
| Disease-specific survival was defined as the time from randomization to death from renal cell carcinoma (RCC). The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. 9999999=wasn't estimable due to no number of events. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline up to death due to RCC (up to approximately 64 months) | |

| | | | | |
|----------------------------------|---------------------------------|---------------------------------|--|--|
| End point values | Atezolizumab | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 390 | 388 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999999 (9999999 to 9999999) | 9999999 (9999999 to 9999999) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Disease-specific survival |
| Comparison groups | Atezolizumab v Placebo |
| Number of subjects included in analysis | 778 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4762 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 1.33 |

Secondary: Percentage of Participants Who Are Alive and IRF-assessed Recurrence Free at Year 1, 2, and 3

| | |
|---|---|
| End point title | Percentage of Participants Who Are Alive and IRF-assessed Recurrence Free at Year 1, 2, and 3 |
| End point description: | |
| IRF-assessed DFS was defined as the percentage of participants being alive and free of recurrence assessed by IRF at Year 1, 2, and 3 after randomization. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 3 years | |

| End point values | Atezolizumab | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 390 | 388 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Year 1 | 81.01 | 76.42 | | |
| Year 2 | 70.40 | 68.22 | | |
| Year 3 | 65.04 | 62.71 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Are Alive and Investigator-assessed Recurrence Free at Year 1, 2, and 3

| | |
|-----------------|--|
| End point title | Percentage of Participants Who Are Alive and Investigator-assessed Recurrence Free at Year 1, 2, and 3 |
|-----------------|--|

End point description:

Investigator-assessed DFS rate was defined as the percentage of participants being alive and free of recurrence assessed by investigator at Year 1, 2, and 3 after randomization. The ITT population was defined as all randomized participants regardless of whether the assigned study treatment was received.

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

End point timeframe:

Up to 3 years

| End point values | Atezolizumab | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 390 | 388 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Year 1 (n=288, 275) | 77.41 | 74.12 | | |
| Year 2 (n=244, 232) | 67.32 | 65.01 | | |
| Year 3 (n=194, 187) | 59.43 | 59.00 | | |

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:

An adverse event (AE) was defined as any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a pharmaceutical product whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as AEs. The safety population included all randomized participants who received any amount of study treatment, regardless of whether a full or partial dose was received.

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

End point timeframe:

From baseline up to death due to any cause (up to approximately 71 months)

| End point values | Atezolizumab | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 390 | 383 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 95.6 | 89.0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of Atezolizumab

| | |
|-----------------|---|
| End point title | Maximum Serum Concentration (Cmax) of Atezolizumab ^[1] |
|-----------------|---|

End point description:

The pharmacokinetic (PK) population included all randomized participants who received any any dose of study treatment and who had at least one measurable post-baseline PK sample available.

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

End point timeframe:

Predose (Hour[hr]0), 0.5 hr after end of infusion (infusion duration=1 hr) on Cycle 1 Day 1; predose (hr 0) on Day 1 of Cycles 2, 3, 4, 8; at treatment discontinuation (up to 1 year); 90-120 days after last dose (last dose = up to 1 year) (Cycle=21 days)

Notes:

[1] - 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: Pharmacokinetics for atezolizumab were determined prior to this study. There are no statistics from this study.

| End point values | Atezolizumab | | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 369 | | | |
| Units: Micrograms per milliliter (ug/mL) | | | | |
| arithmetic mean (standard deviation) | 399 (± 138) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Drug Antibodies (ADA) to Atezolizumab

| | |
|-----------------|---|
| End point title | Percentage of Participants With Anti-Drug Antibodies (ADA) to Atezolizumab ^[2] |
|-----------------|---|

End point description:

The immunogenicity analysis population will consist of all participants with at least one ADA assessment for atezolizumab. The post-baseline ADA evaluable population included all participants who received at least one dose of atezolizumab and with at least one post-dose ADA assessment.

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

End point timeframe:

Predose (hr 0) on Day 1 of Cycles 1, 2, 3, 4, 8; at treatment discontinuation (up to 1 year); 90-120 days after last dose (last dose = up to 1 year) (Cycle=21 days)

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: There are no statistics from this study.

| End point values | Atezolizumab | | | |
|-----------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 390 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Baseline | 1.8 | | | |

| | | | | |
|-------------------------|------|--|--|--|
| Treatment Emergent ADAs | 26.4 | | | |
|-------------------------|------|--|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Serum Concentration (Cmin) of Atezolizumab

| | |
|-----------------|---|
| End point title | Minimum Serum Concentration (Cmin) of Atezolizumab ^[3] |
|-----------------|---|

End point description:

The PK population included all randomized participants who received any any dose of study treatment and who had at least one measurable post-baseline PK sample available.

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

End point timeframe:

Predose (Hour[hr]0), 0.5 hr after end of infusion (infusion duration=1 hr) on Cycle 1 Day 1; predose (hr 0) on Day 1 of Cycles 2, 3, 4, 8; at treatment discontinuation (up to 1 year); 90-120 days after last dose (last dose = up to 1 year) (Cycle=21 days)

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: Pharmacokinetics for atezolizumab were determined prior to this study. There are no statistics from this study.

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Atezolizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 85 | | | |
| Units: ug/mL | | | | |
| arithmetic mean (standard deviation) | 34.1 (± 30.1) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to 90 days after last dose of study drug or until initiation of new systemic anti-cancer therapy, whichever occurs first (last dose = up to approximately 71 months)

Adverse event reporting additional description:

The safety population included all randomized participants who received any amount of study treatment, regardless of whether a full or partial dose was received.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Atezolizumab |
|-----------------------|--------------|

Reporting group description:

Participants received atezolizumab 1200 milligrams (mg) intravenous (IV) infusion every 3 weeks (q3w) for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first).

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received placebo matching to atezolizumab q3w for 16 cycles (each cycle=21 days) or 1 year (whichever occurred first)

| Serious adverse events | Atezolizumab | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 69 / 390 (17.69%) | 46 / 383 (12.01%) | |
| number of deaths (all causes) | 57 | 55 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gallbladder cancer | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder papilloma | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myeloid leukaemia | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Colorectal adenoma | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Vasculitis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 390 (0.51%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 390 (0.77%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Death | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ulcer | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza like illness | | | |
| subjects affected / exposed | 2 / 390 (0.51%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyp | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Immune-mediated adverse reaction | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic immune activation | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|---|-----------------|-----------------|--|
| disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 390 (0.77%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural fever | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 390 (0.26%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 390 (0.51%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 2 / 383 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 2 / 383 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tremor | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Axonal neuropathy | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 2 / 390 (0.51%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 2 / 383 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 390 (0.51%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Blindness unilateral | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 390 (0.51%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 390 (0.77%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eosinophilic colitis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 3 / 390 (0.77%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 2 / 383 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 390 (0.00%) | 3 / 383 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis psoriasiform | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psoriasis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 3 / 383 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basedow's disease | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Musculoskeletal and connective tissue disorders | | | |
| Polymyositis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myositis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flank pain | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Herpes ophthalmic | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Pharyngeal abscess | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 390 (0.77%) | 2 / 383 (0.52%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 390 (1.03%) | 3 / 383 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 390 (0.26%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis aseptic | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal infection | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 2 / 383 (0.52%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Salpingitis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal candidiasis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 390 (0.00%) | 1 / 383 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mediastinitis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 390 (0.26%) | 0 / 383 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 5 / 390 (1.28%) | 2 / 383 (0.52%) | |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Atezolizumab | Placebo | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 329 / 390 (84.36%) | 290 / 383 (75.72%) | |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 11 / 390 (2.82%) | 21 / 383 (5.48%) | |
| occurrences (all) | 13 | 22 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 29 / 390 (7.44%) | 29 / 383 (7.57%) | |
| occurrences (all) | 36 | 39 | |
| Alanine aminotransferase increased | | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed occurrences (all) | 26 / 390 (6.67%) 29 | 12 / 383 (3.13%) 15 | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 19 / 390 (4.87%) 20 | 36 / 383 (9.40%) 41 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 29 / 390 (7.44%) 30 51 / 390 (13.08%) 65 | 29 / 383 (7.57%) 33 49 / 383 (12.79%) 72 | |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) | 41 / 390 (10.51%) 44 110 / 390 (28.21%) 145 29 / 390 (7.44%) 39 21 / 390 (5.38%) 26 36 / 390 (9.23%) 47 | 16 / 383 (4.18%) 32 93 / 383 (24.28%) 124 18 / 383 (4.70%) 27 17 / 383 (4.44%) 19 26 / 383 (6.79%) 28 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 24 / 390 (6.15%) 29 | 14 / 383 (3.66%) 15 | |
| Gastrointestinal disorders Vomiting | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 18 / 390 (4.62%) | 28 / 383 (7.31%) | |
| occurrences (all) | 19 | 29 | |
| Dry mouth | | | |
| subjects affected / exposed | 26 / 390 (6.67%) | 6 / 383 (1.57%) | |
| occurrences (all) | 29 | 6 | |
| Abdominal pain | | | |
| subjects affected / exposed | 26 / 390 (6.67%) | 23 / 383 (6.01%) | |
| occurrences (all) | 31 | 24 | |
| Diarrhoea | | | |
| subjects affected / exposed | 85 / 390 (21.79%) | 79 / 383 (20.63%) | |
| occurrences (all) | 128 | 125 | |
| Nausea | | | |
| subjects affected / exposed | 46 / 390 (11.79%) | 54 / 383 (14.10%) | |
| occurrences (all) | 64 | 77 | |
| Constipation | | | |
| subjects affected / exposed | 26 / 390 (6.67%) | 26 / 383 (6.79%) | |
| occurrences (all) | 29 | 28 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 51 / 390 (13.08%) | 48 / 383 (12.53%) | |
| occurrences (all) | 63 | 51 | |
| Dyspnoea | | | |
| subjects affected / exposed | 26 / 390 (6.67%) | 16 / 383 (4.18%) | |
| occurrences (all) | 34 | 18 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 25 / 390 (6.41%) | 14 / 383 (3.66%) | |
| occurrences (all) | 33 | 17 | |
| Pruritus | | | |
| subjects affected / exposed | 74 / 390 (18.97%) | 48 / 383 (12.53%) | |
| occurrences (all) | 94 | 61 | |
| Rash | | | |
| subjects affected / exposed | 46 / 390 (11.79%) | 20 / 383 (5.22%) | |
| occurrences (all) | 55 | 24 | |
| Endocrine disorders | | | |

| | | | |
|---|--------------------------|-------------------------|--|
| Hyperthyroidism subjects affected / exposed occurrences (all) | 20 / 390 (5.13%) 21 | 4 / 383 (1.04%) 4 | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 56 / 390 (14.36%) 62 | 12 / 383 (3.13%) 13 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 43 / 390 (11.03%) 52 | 45 / 383 (11.75%) 55 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 18 / 390 (4.62%) 20 | 20 / 383 (5.22%) 24 | |
| Arthralgia subjects affected / exposed occurrences (all) | 78 / 390 (20.00%) 101 | 57 / 383 (14.88%) 75 | |
| Myalgia subjects affected / exposed occurrences (all) | 35 / 390 (8.97%) 40 | 25 / 383 (6.53%) 39 | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 23 / 390 (5.90%) 30 | 26 / 383 (6.79%) 32 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 33 / 390 (8.46%) 39 | 27 / 383 (7.05%) 31 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 21 / 390 (5.38%) 26 | 16 / 383 (4.18%) 16 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 15 September 2016 | The following changes were made: [1] The Leibovich scoring system as an eligibility criterion was replaced; [2] The study population was broadened; [3] The intended sample size was adjusted; [4] The definition of a DFS event included new primary renal cell carcinoma (RCC); [5] Radiographic scans performed as part of surveillance for RCC recurrence would be submitted to central assessment for potential independent review; [6] A sample of RCC tumor with the highest tumor grade would be submitted for central review; [7] A safety evaluation visit was added at 3 months after the last dose of study treatment; [8] Detailed guidelines for investigator determination of RCC disease recurrence were added; [9] Updated safety data from a Phase Ia Study was included in the protocol; [10] DFS in participants whose tumors express IHC IC1/2/3 was added as a secondary endpoint; [11] Randomization stratification factors were changed to reflect the updated participant population; [12] The number of study sites increased; [13] Instructions for emergency unblinding of treatment assignment were provided; [14] The definition of a positive surgical margin was clarified; [15] Guidance was provided regarding the eligibility of participants with small pulmonary nodules; [16] Exclusion criteria were updated; [17] The frequency of surveillance imaging for RCC recurrence was reduced; [18] Clarification was made regarding thyroid-function testing; [19] Epstein-Barr Virus (EBV) screening sample collection was removed; [20] The timing of patient-reported outcome evaluations was clarified; [21] The instructions for the reporting of infusion-related reactions were modified; [22] The back-up Medical Monitor changed; [23] The definition of sarcomatoid RCC was clarified; [24] Additional minor changes were made to improve clarity and consistency. |
| 16 December 2016 | The following changes were made: [1] The method of assessment of the primary endpoint was changed; [2] It was specified that tumor assessments should continue until disease recurrence; [3] Assessment of imaging data by independent central radiologic review was required for confirmation of disease-free status at baseline; [4] The frequency of surveillance imaging for RCC recurrence after Year 4 was increased from annually to every 6 months; [5] Clarification that the level of stratification factors could be combined for analysis purposes; [6] Clarification that prospective protocol deviations were not allowed; [7] Pregnancy testing frequency was increased to every cycle and at the first post-treatment visit; [8] Details of the Medical Monitor and back-up Medical Monitor were updated; [9] The imaging and biopsy requirements for confirmation of disease recurrence were updated; [10] Additional minor changes were made to improve clarity and consistency. |
| 01 March 2018 | The following updates were made: [1] Section 5.1.1 was amended to align with current atezolizumab risk language; [2] Appendix 11 was added so there was no longer a need to consult the Atezolizumab Investigator's Brochure for management guidelines; [3] Additional minor changes were made to improve clarity and consistency. |
| 20 September 2018 | The following changes were made: [1] The control (placebo) arm median disease-free survival (mDFS) assumption was modified from 36 to 47 months, and the control arm median overall survival (OS) assumption was modified from 81.4 to 100 months; [2] Eligibility criteria was modified; [3] The role of the independent Data Monitoring Committee (iDMC) was amended; [4] 1- and 2-year IRF-assessed DFS rate and 1- and 2-year investigator-assessed DFS rate were added as secondary efficacy endpoints; [5] Inclusion criterion were modified; [6] The exclusionary time periods were amended; [7] Information regarding blinding of treatment assignment and circumstances for unblinding were updated; [8] |

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| 05 December 2018 | The following changes were made: [1] Specified when ECG recordings were required; [2] Exclusion criterion were clarified; [3] Stated that premedication is "not routinely recommended" instead of "not permitted;" [4] Median disease-free survival (mDFS) assumption of the control arm was amended; [5] It was clarified that the Unblinded Medical Monitor would not be directly involved in the conduct of the clinical study; [6] The control arm mDFS and OS assumptions were modified; [7] Eligibility criteria were modified; [8] The role of the independent Data Monitoring Committee was amended; [9] 1- and 2-year IRF-assessed DFS rate and 1- and 2-year investigator-assessed DFS rate were added as secondary efficacy endpoints; [10] The exclusionary time periods were amended; [11] Information regarding blinding of treatment and unblinding was updated; [12] Clarification was made regarding the administration of infusions and timing of vital sign measurements relative; [13] Clarification of various assessments; [14] Clarification regarding timepoints for completion of patient-reported outcome questionnaires; [15] Instructions about participant withdrawal from the RBR after site closure were modified; [16] Lists of risks for atezolizumab and guidelines for managing participants who experience atezolizumab-associated AEs was revised; [17] Information regarding systemic immune activation was amended; [18] The reporting of the term "sudden death" was updated; [19] Event reporting for hospitalization was clarified; [20] Back-up and Unblinded Medical Monitor information was updated; [21] Additional language was added or updated for clarification; [22] Guidelines for the assessment of renal cell carcinoma- were amended; [23] Additional minor changes were made to improve clarity and consistency. |
| 15 February 2020 | The following changes were made: [1] "Immune-related" was changed to "immune-mediated" when describing events associated with atezolizumab; [2] Exploratory study objectives were updated; [3] Language was added for clarification; [4] The list of atezolizumab risks was updated; [5] Systemic immune activation was replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab; [6] Medical Monitor information was updated; [7] Clarification was provided on the reporting of all deaths after the AE reporting period; [8] Definition of local recurrence was updated; [9] Additional details were provided on the planned exploratory subgroup analysis of participants with tumor Fuhrman Grade 4 or sarcomatoid histology; [10] The requirement for use of a tourniquet was removed; [11] The atezolizumab AE management guidelines were revised; [12] The management guidelines for infusion-related reactions associated with atezolizumab were updated; [13] Guidelines for managing participants who experienced atezolizumab-associated AE were revised to include myositis; [14] Additional minor changes were made to improve clarity and consistency. |
| 07 February 2021 | The following changes were made: [1] Language was added to clarify endpoints associated with secondary efficacy and exploratory objectives; [2] Statistical methods updated to remove the planned interim DFS analysis and to update the total OS analyses; [3] COVID-specific information and risk language was included; [4] Clarified that the iDMC scope of evaluation was for safety data only; [5] Clarified that unblinding of treatment assignment would occur after the primary analysis of DFS; [6] Language in relation to AE reporting associated with PRO data was removed; [7] Back-up medical monitor information was updated; [8] Detailed updates associated with the removal of the planned interim DFS analysis; [9] Incorporate language associated with a sensitivity analysis that will be conducted for IRF-assessed DFS; [10] Atezo protocol SCAR language updated; [11] HLH and MAS replaced systemic inflammatory response syndrome on the list of atezolizumab-associated AEs of special interest (AESIs); [12] The management guidelines for HLH and MAS were modified; [13] Clarified that AEs associated with a special situation that also qualify as AESIs should be reported within 24 hours; [14] Clarified that sites are not expected to review the PRO data for AEs; [15] Female participants were to inform the investigator if they became pregnant per ICF instructions; [16] Correction to the Roche policy on data sharing; [17] The list of approved indications for atezolizumab was updated; [18] The management guidelines for Grade 4 myositis were removed; [19] ATA (anti-therapeutic antibody) was updated to ADA (anti-drug antibody); [20] "Immunerelated" was changed to "immune-mediated" when describing events associated with atezolizumab; [21] Additional minor changes were made to improve clarity and consistency. |

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| 12 November 2021 | The following changes were made: [1] The protocol was amended to change the primary endpoint of IRF-assessed DFS to investigator-assessed DFS; [2] Benefit-risk assessment and guidance on concomitant administration of coronavirus disease 2019 vaccines with atezolizumab were modified; [3] Language was updated to change the endpoint of IRF-assessed DFS to investigator-assessed DFS; [4] The secondary efficacy endpoint of investigator-assessed DFS was changed to IRF-assessed DFS; [5] A new secondary endpoint of IRF-assessed event-free survival (EFS) was added; [6] The endpoint for immunogenicity objective, "To evaluate the immune response to atezolizumab" was updated; [7] The definition of "Distant metastasis-free survival" in secondary efficacy objective endpoint was updated; [8] One exploratory endpoint was removed; [9] The responsibilities of the Principal Investigator and the role of the Medical Monitor were clarified; [10] Language was updated to clarify the use of public record searches for survival follow-up following withdrawal of consent; [11] The Medical Monitor information was updated; [12] The name of "Serious Adverse Events (SAE)/AESI Reporting Form" was updated; [13] Language was updated to include time to clinically confirmed deterioration analysis to allow for analyzing all FKSI-19 data captured; [14] The medical term "primary biliary cirrhosis" was replaced by the term "primary biliary cholangitis;" [15] The adverse event management guidelines was updated; [16] The management guidelines referencing Grade 4 myositis were removed; [17] Additional minor changes were made to improve clarity and consistency. |
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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 terminate this study before the protocol-defined end-of-study, as permitted per protocol.

Notes: