



Clinical trial results:

A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) as Adjuvant Therapy After Definitive Local Therapy in Patients With High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2017-003302-40 |
| Trial protocol | DE ES GB PL FR BE PT HU IT |
| Global end of trial date | 06 March 2024 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 02 October 2024 |
| First version publication date | 02 October 2024 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | WO40242 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03452137 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | F. Hoffmann-La Roche Ltd. |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4058 |
| Public contact | F. Hoffmann-La Roche Ltd., F. Hoffmann-La Roche Ltd., +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche Ltd., F. Hoffmann-La Roche Ltd., +41 616878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

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|--|----|
| 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 | 06 March 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 September 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 March 2024 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The study aims to evaluate the efficacy of atezolizumab compared with placebo after definitive local therapy in participants with high-risk locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 03 April 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 | Australia: 7 |
| Country: Number of subjects enrolled | Belgium: 2 |
| Country: Number of subjects enrolled | Brazil: 20 |
| Country: Number of subjects enrolled | Canada: 3 |
| Country: Number of subjects enrolled | China: 8 |
| Country: Number of subjects enrolled | Germany: 9 |
| Country: Number of subjects enrolled | Spain: 24 |
| Country: Number of subjects enrolled | France: 35 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Hungary: 5 |
| Country: Number of subjects enrolled | India: 16 |
| Country: Number of subjects enrolled | Italy: 21 |
| Country: Number of subjects enrolled | Japan: 53 |
| Country: Number of subjects enrolled | Korea, Republic of: 10 |
| Country: Number of subjects enrolled | Poland: 17 |
| Country: Number of subjects enrolled | Portugal: 27 |
| Country: Number of subjects enrolled | Russian Federation: 39 |
| Country: Number of subjects enrolled | Thailand: 16 |
| Country: Number of subjects enrolled | Türkiye: 7 |
| Country: Number of subjects enrolled | Taiwan: 25 |
| Country: Number of subjects enrolled | Ukraine: 19 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 28 |
| Country: Number of subjects enrolled | South Africa: 5 |
| Worldwide total number of subjects | 406 |
| EEA total number of subjects | 140 |

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) | 297 |
| From 65 to 84 years | 109 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study across 128 investigative sites in 23 countries from 03 April 2018 to 06 March 2024.

Pre-assignment

Screening details:

A total of 406 participants with locally advanced squamous cell carcinoma of the head and neck (SCCHN) were randomized in 1:1 ratio to receive either atezolizumab or placebo.

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, Monitor, Carer, Data analyst, Assessor |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Participants received atezolizumab matching placebo, intravenous (IV) infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first.

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

Dosage and administration details:

Placebo, on Day 1 of each 21-day cycle as IV infusion for up to Cycle 16 or up to 1 year.

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

Arm description:

Participants received atezolizumab 1200 milligrams (mg), IV infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Atezolizumab |
| Investigational medicinal product code | RO5541267 |
| Other name | Tecentriq, MPDL3280A |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Atezolizumab, 1200 mg, on Day 1 of each 21-day cycle as IV infusion for up to Cycle 16 or up to 1 year.

| Number of subjects in period 1 | Placebo | Atezolizumab |
|--|---------|--------------|
| Started | 203 | 203 |
| Received at Least One Dose of Study Drug | 203 | 202 |
| Completed | 0 | 0 |
| Not completed | 203 | 203 |
| Adverse event, serious fatal | 67 | 70 |
| Consent withdrawn by subject | 12 | 9 |
| Physician decision | - | 1 |
| Study Terminated by Sponsor | 120 | 121 |
| Lost to follow-up | 4 | 2 |

Baseline characteristics

Reporting groups

| | |
|--|--------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received atezolizumab matching placebo, intravenous (IV) infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first. | |
| Reporting group title | Atezolizumab |
| Reporting group description: | |
| Participants received atezolizumab 1200 milligrams (mg), IV infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first. | |

| Reporting group values | Placebo | Atezolizumab | Total |
|------------------------|---------|--------------|-------|
| Number of subjects | 203 | 203 | 406 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|-------|-----|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 57.7 | 59.4 | |
| standard deviation | ± 10.1 | ± 8.5 | - |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 29 | 35 | 64 |
| Male | 174 | 168 | 342 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 1 | 1 |
| Asian | 61 | 68 | 129 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 1 | 1 | 2 |
| White | 135 | 121 | 256 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 6 | 12 | 18 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 13 | 11 | 24 |
| Not Hispanic or Latino | 181 | 183 | 364 |
| Unknown or Not Reported | 9 | 9 | 18 |
| Human papilloma virus (HPV) Status | | | |
| Units: Subjects | | | |
| Negative | 166 | 168 | 334 |
| Positive | 37 | 35 | 72 |
| Type of Definitive Local Therapy | | | |
| Units: Subjects | | | |
| Primary Surgery | 78 | 79 | 157 |
| No Primary Surgery | 125 | 124 | 249 |

| | | | |
|--|-----|-----|-----|
| Response to Definitive Local Therapy | | | |
| Responses were assessed according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1). | | | |
| Units: Subjects | | | |
| Complete Response (CR) | 170 | 170 | 340 |
| Partial Response (PR) or Stable Disease (SD) | 33 | 33 | 66 |

End points

End points reporting groups

| | |
|--|--------------|
| Reporting group title | Placebo |
| Reporting group description: Participants received atezolizumab matching placebo, intravenous (IV) infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first. | |
| Reporting group title | Atezolizumab |
| Reporting group description: Participants received atezolizumab 1200 milligrams (mg), IV infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first. | |

Primary: Investigator-Assessed Event-Free Survival (INV-assessed EFS)

| | |
|--|--|
| End point title | Investigator-Assessed Event-Free Survival (INV-assessed EFS) |
| End point description: EFS=time from randomization to first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression [per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)] per assessment by investigator, or death from any cause, whichever occurred first. Progressive disease (PD)=at least a 20% increase in the sum of diameters (SOD) of target lesions, taking as reference the smallest SOD on study (including baseline). Participants without disease recurrence, progression or death at the time of analysis were censored at the time of the last tumor assessment. EFS was estimated using the Kaplan-Meier (KM) method. 99999=The upper limit of the 95% CI was not estimable for INV-EFS because there was an insufficient number of events. ITT population=all randomized participants, regardless of whether they received any of the assigned treatment. | |
| End point type | Primary |
| End point timeframe: Randomization to the first documented disease recurrence, disease progression or death from any cause, whichever occurs first (up to 5 years) | |

| End point values | Placebo | Atezolizumab | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 | 203 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 52.73 (41.43 to 99999) | 59.47 (46.75 to 99999) | | |

Statistical analyses

| | |
|--|-------------------------|
| Statistical analysis title | Placebo vs Atezolizumab |
| Statistical analysis description: Stratified Analysis: The stratification factors were response to definitive local therapy, human papillomavirus (HPV) status and type of definitive local therapy as per interactive voice or web-based response system (IxRS). | |
| Comparison groups | Atezolizumab v Placebo |

| | |
|---|-------------------|
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6804 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.26 |

Secondary: Independent Review Facility (IRF) Assessed EFS

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|------------------------|--|
| End point title | Independent Review Facility (IRF) Assessed EFS |
| End point description: | EFS was defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) per assessment by IRF, or death from any cause, whichever occurred first. PD was defined as at least a 20% increase in the SOD of target lesions, taking as reference the smallest SOD on study (including baseline). Participants without disease recurrence, progression or death at the time of analysis were censored at the time of the last tumor assessment. EFS was estimated using the Kaplan-Meier method. ITT population included all randomized participants, regardless of whether they received any of the assigned treatment. 99999= the upper limit of the 95% CI was not estimable for IRF-EFS because there was an insufficient number of events. |
| End point type | Secondary |
| End point timeframe: | Randomization to the first documented disease recurrence, disease progression or death from any cause, whichever occurs first (up to 5 years) |

| End point values | Placebo | Atezolizumab | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 | 203 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 52.73 (43.10 to 99999) | 59.47 (45.17 to 99999) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Placebo vs Atezolizumab |
| Statistical analysis description: | Stratified Analysis: The stratification factors were response to definitive local therapy, HPV status and type of definitive local therapy as per interactive voice or web-based response system (IxRS). |
| Comparison groups | Placebo v Atezolizumab |

| | |
|---|-------------------|
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9115 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.32 |

Secondary: Overall Survival (OS)

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|---|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| OS was defined as the time from randomization to death from any cause. Data from participants who were alive at the time of the analysis was censored as of the last date they were known to be alive. OS was estimated using the Kaplan-Meier method. 99999= The median and lower and upper limits of the 95% CI were not estimable for OS because there was an insufficient number of events. ITT population included all randomized participants, regardless of whether they received any of the assigned treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| Randomization to death from any cause (up to 5 years, 5 months) | |

| End point values | Placebo | Atezolizumab | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 | 203 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (59.47 to 99999) | | |

Statistical analyses

| | |
|--|-------------------------|
| Statistical analysis title | Placebo vs Atezolizumab |
| Statistical analysis description: | |
| Stratified Analysis: The stratification factors were response to definitive local therapy, HPV status and type of definitive local therapy as per interactive voice or web-based response system (IxRS). | |
| Comparison groups | Atezolizumab v Placebo |

| | |
|---|-------------------|
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8371 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.36 |

Secondary: Percentage of Participants Event-Free for IRF-assessed EFS at 1, 2, 3, and 4 Years

| | |
|-----------------|--|
| End point title | Percentage of Participants Event-Free for IRF-assessed EFS at 1, 2, 3, and 4 Years |
|-----------------|--|

End point description:

EFS=time from randomization to first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion/development of distant metastasis) or disease progression (per RECIST v1.1) per assessment by IRF or death from any cause, whichever occurred first. PD=at least a 20% increase in SOD of target lesions, taking as reference smallest SOD on study (including baseline). Participants without disease recurrence, progression/death at time of analysis were censored at time of last tumor assessment. KM approach was used to estimate percentage of participants who were event-free for EFS at 1, 2, 3 & 4 years. ITT population=all randomized participants, regardless of whether they received any of the assigned treatment. n=number analyzed per timepoint are unique number of participants out of all assessed participants who remain at risk for an EFS event at that timepoint. Different participants may have contributed data for each timepoint.

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

End point timeframe:

From randomization to EFS event or date last known to be alive and event-free at 1, 2, 3, and 4 years

| End point values | Placebo | Atezolizumab | | |
|-----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 | 203 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| 1 Year (n=143, 142) | 72.59 (66.41 to 78.77) | 71.92 (65.68 to 78.16) | | |
| 2 Year (n=124, 128) | 65.85 (59.25 to 72.46) | 66.31 (59.73 to 72.89) | | |
| 3 Year (n=108, 115) | 59.87 (52.99 to 66.76) | 61.07 (54.25 to 67.88) | | |
| 4 Year (n=63, 66) | 54.71 (47.51 to 61.90) | 54.72 (47.52 to 61.91) | | |

Statistical analyses

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|--|-------------------------------|
| Statistical analysis title | Placebo vs Atezolizumab |
| Statistical analysis description: | |
| Difference in EFS Event-Free Rates at 1 year | |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8816 |
| Method | Z test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | -0.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.45 |
| upper limit | 8.11 |

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|---|-------------------------------|
| Statistical analysis title | Placebo vs Atezolizumab |
| Statistical analysis description: | |
| Difference in EFS Event-Free Rates at 2 years | |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9234 |
| Method | Z test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.86 |
| upper limit | 9.78 |

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|---|-------------------------------|
| Statistical analysis title | Placebo vs Atezolizumab |
| Statistical analysis description: | |
| Difference in EFS Event-Free Rates at 3 years | |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.809 |
| Method | Z test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 1.19 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.49 |
| upper limit | 10.88 |

| | |
|---|-------------------------------|
| Statistical analysis title | Placebo vs Atezolizumab |
| Statistical analysis description: | |
| Difference in EFS Event-Free Rates at 4 years | |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9985 |
| Method | Z test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.17 |
| upper limit | 10.19 |

Secondary: Percentage of Participants Event-Free for INV-assessed EFS at 1, 2, 3, and 4 Years

| | |
|-----------------|--|
| End point title | Percentage of Participants Event-Free for INV-assessed EFS at 1, 2, 3, and 4 Years |
|-----------------|--|

End point description:

EFS=time from randomization to first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion/development of distant metastasis)/disease progression (per RECIST v1.1) per investigator or death from any cause, whichever occurred first. PD=at least a 20% increase in SOD of target lesions, taking as reference the smallest SOD on study (including baseline). Participants without disease recurrence, progression/death at time of analysis were censored at time of last tumor assessment. KM approach was used to estimate percentage of participants who were event-free for EFS at 1, 2, 3 & 4 years. ITT population=all randomized participants, regardless of whether they received any of the assigned treatment. n=number analyzed per timepoint are unique number of participants out of all the assessed participants who remain at risk for an EFS event at that timepoint. Different participants may have contributed data for each timepoint.

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

End point timeframe:

From randomization to EFS event or date last known to be alive and event-free at 1, 2, 3, and 4 years

| End point values | Placebo | Atezolizumab | | |
|-----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 | 203 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| 1 Year (n=143, 151) | 70.84 (64.58 to 77.10) | 76.01 (70.09 to 81.93) | | |
| 2 Year (n=124, 131) | 63.81 (57.17 to 70.45) | 67.41 (60.90 to 73.92) | | |
| 3 Year (n=110, 118) | 58.57 (51.73 to 65.41) | 61.71 (54.94 to 68.49) | | |
| 4 Year (n=64, 70) | 55.51 (48.49 to 62.52) | 56.82 (49.75 to 63.88) | | |

Statistical analyses

| Statistical analysis title | Placebo vs Atezolizumab |
|--|-------------------------------|
| Statistical analysis description: | |
| Difference in EFS Event-Free Rates at 1 year | |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2393 |
| Method | Z test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 5.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.44 |
| upper limit | 13.79 |

| Statistical analysis title | Placebo vs Atezolizumab |
|---|-------------------------------|
| Statistical analysis description: | |
| Difference in EFS Event-Free Rates at 4 years | |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7967 |
| Method | Z test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 1.31 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.64 |
| upper limit | 11.26 |

| | |
|---|-------------------------------|
| Statistical analysis title | Placebo vs Atezolizumab |
| Statistical analysis description: | |
| Difference in EFS Event-Free Rates at 3 years | |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5222 |
| Method | Z test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 3.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.49 |
| upper limit | 12.77 |

| | |
|---|-------------------------------|
| Statistical analysis title | Placebo vs Atezolizumab |
| Statistical analysis description: | |
| Difference in EFS Event-Free Rates at 2 years | |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4472 |
| Method | Z test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 3.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.69 |
| upper limit | 12.9 |

| | |
|---|---|
| Secondary: Percentage of Participants Event-Free for OS at 2, 3, and 5 Years | |
| End point title | Percentage of Participants Event-Free for OS at 2, 3, and 5 Years |

End point description:

OS was defined as the time from randomization to death from any cause. Data from participants who were alive at the time of the analysis was censored as of the last date they were known to be alive. Kaplan-Meier approach was used to estimate the percentage of participants who were event-free for OS at 2, 3 and 5 years. ITT population included all randomized participants, regardless of whether they received any of the assigned treatment. n indicates that number analyzed per timepoint are unique number of participants out of all the assessed participants who remain at risk for an OS event at that timepoint. Different participants may have contributed data for each timepoint.

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

End point timeframe:

From randomization to OS event or date last known to be alive at 2, 3, and 5 Years

| End point values | Placebo | Atezolizumab | | |
|-----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 | 203 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| 2 Year (n=157, 163) | 79.23 (73.64 to 84.82) | 82.00 (76.68 to 87.33) | | |
| 3 Year (n=143, 140) | 73.59 (67.48 to 79.70) | 72.34 (66.11 to 78.56) | | |
| 5 Year (n=6, 6) | 62.00 (53.46 to 70.55) | 60.93 (48.01 to 73.86) | | |

Statistical analyses

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Placebo vs Atezolizumab |
|-----------------------------------|-------------------------|

Statistical analysis description:

Difference in OS Event-Free Rates at 2 years

| | |
|---|-------------------------------|
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4819 |
| Method | Z test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | 2.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.95 |
| upper limit | 10.49 |

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Placebo vs Atezolizumab |
|-----------------------------------|-------------------------|

Statistical analysis description:

Difference in OS Event-Free Rates at 5 years

| | |
|---|-------------------------------|
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8924 |
| Method | Z test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | -1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.56 |
| upper limit | 14.42 |

| | |
|--|-------------------------------|
| Statistical analysis title | Placebo vs Atezolizumab |
| Statistical analysis description: | |
| Difference in OS Event-Free Rates at 3 years | |
| Comparison groups | Placebo v Atezolizumab |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7783 |
| Method | Z test |
| Parameter estimate | Difference in Event Free Rate |
| Point estimate | -1.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.97 |
| upper limit | 7.47 |

Secondary: Change From Baseline in Physical Function (PF) as Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Core 30 (EORTC-QLQ-C30) Score

| | |
|-----------------|---|
| End point title | Change From Baseline in Physical Function (PF) as Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Core 30 (EORTC-QLQ-C30) Score |
|-----------------|---|

End point description:

EORTC QLQ-C30 scale uses 30 questions to assess participant functioning (physical, emotional, role, cognitive & social), symptoms (fatigue, nausea & vomiting, pain), global health/quality of life(QoL) & 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, & financial difficulties). Change in PF was assessed using PF scale: participant responses to 5 questions about daily activities (strenuous activities, long walks, short walks, bed/chair rest & needing help with eating, dressing, washing themselves/using toilet) was scored on 4-point scale (1=Not at All to 4=Very Much). Scores were linearly transformed on a scale of 0-100. High score=worst functioning. ITT population=all randomized participants, regardless of whether they received any of assigned treatment. Number analyzed=number of participants with data available for analysis. n=number of participants with data available for analysis at specified timepoint. 9999=No participants were analyzed at this timepoint.

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

End point timeframe:

Baseline, Day 1 of Cycles 2 to 16 (Cycle length = 21 days); study discontinuation visit (up to 1 year);
Follow-up approximately every 3 months until disease recurrence or progression (up to approximately 4.5 years)

| End point values | Placebo | Atezolizumab | | |
|--|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 201 | 200 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (Cycle 1 Day 1) (n=201, 200) | 82.78 (± 16.36) | 83.46 (± 16.79) | | |
| Change at Cycle 2 Day 1 (n=195, 193) | 2.40 (± 11.09) | -0.58 (± 10.54) | | |
| Change at Cycle 3 Day 1 (n= 194, 186) | 3.75 (± 12.03) | -0.13 (± 12.62) | | |
| Change at Cycle 4 Day 1 (n=177, 179) | 2.90 (± 13.00) | 0.77 (± 13.42) | | |
| Change at Cycle 5 Day 1 (n=171, 168) | 4.69 (± 13.86) | 1.60 (± 12.15) | | |
| Change at Cycle 6 Day 1 (n=169, 162) | 4.03 (± 12.76) | 2.18 (± 13.87) | | |
| Change at Cycle 7 Day 1 (n=162, 154) | 4.33 (± 13.07) | 3.56 (± 13.68) | | |
| Change at Cycle 8 Day 1 (n= 156, 151) | 4.63 (± 13.07) | 3.19 (± 13.71) | | |
| Change at Cycle 9 Day 1 (n=152, 147) | 4.62 (± 13.86) | 2.96 (± 14.41) | | |
| Change at Cycle 10 Day 1 (n=148, 143) | 4.41 (± 14.30) | 2.12 (± 14.22) | | |
| Change at Cycle 11 Day 1 (n=145, 139) | 3.82 (± 14.20) | 3.69 (± 12.43) | | |
| Change at Cycle 12 Day 1 (n=143, 139) | 4.35 (± 15.23) | 3.05 (± 14.89) | | |
| Change at Cycle 13 Day 1 (n=138, 136) | 5.62 (± 13.63) | 3.30 (± 15.02) | | |
| Change at Cycle 14 Day 1 (n=134, 129) | 6.73 (± 13.67) | 3.20 (± 13.36) | | |
| Change at Cycle 15 Day 1 (n=133, 124) | 6.13 (± 13.11) | 3.99 (± 12.92) | | |
| Change at Cycle 16 Day 1 (n=122, 116) | 5.92 (± 14.85) | 4.11 (± 12.88) | | |
| Change at Study Discontinuation (n=181, 175) | 2.94 (± 16.52) | 2.70 (± 14.20) | | |
| Change at Follow Up 1 (n=51, 50) | 1.47 (± 16.36) | -6.63 (± 24.41) | | |
| Change at Follow Up 2 (n=42, 44) | -1.15 (± 18.10) | 0.19 (± 17.34) | | |
| Change at Follow Up 3 (n=35, 33) | -0.81 (± 17.17) | 2.68 (± 18.75) | | |
| Change at Follow Up 4 (n=36, 28) | -1.90 (± 18.62) | -2.56 (± 28.57) | | |
| Change at Follow Up 5 (n=30, 21) | -2.00 (± 26.21) | -6.03 (± 35.58) | | |
| Change at Follow Up 6 (n=30, 18) | -3.61 (± 18.08) | -3.24 (± 23.84) | | |
| Change at Follow Up 7 (n=20, 13) | -6.75 (± 21.85) | 1.54 (± 24.82) | | |
| Change at Follow Up 8 (n=20, 11) | -13.08 (± 28.96) | 1.36 (± 33.11) | | |
| Change at Follow Up 9 (n=11, 9) | 2.88 (± 14.38) | 4.63 (± 17.36) | | |
| Change at Follow Up 10 (n=7, 8) | -16.43 (± 32.50) | 3.33 (± 13.80) | | |
| Change at Follow Up 11 (n=10, 4) | -10.00 (± 35.31) | -16.67 (± 24.65) | | |
| Change at Follow Up 12 (n=6, 4) | -6.67 (± 8.43) | 0.00 (± 14.40) | | |
| Change at Follow Up 13 (n=7, 3) | -5.71 (± 7.13) | 4.44 (± 10.18) | | |

| | | | | |
|---------------------------------|-----------------------|--------------------|--|--|
| Change at Follow Up 14 (n=3, 1) | -17.78 (\pm 42.86) | -6.67 (\pm 0) | | |
| Change at Follow Up 15 (n=4, 0) | -5.00 (\pm 6.38) | 9999 (\pm 9999) | | |
| Change at Follow Up 16 (n=3, 0) | 2.22 (\pm 10.18) | 9999 (\pm 9999) | | |
| Change at Follow Up 17 (n=2, 0) | -3.33 (\pm 4.71) | 9999 (\pm 9999) | | |
| Change at Follow Up 18 (n=2, 0) | 13.33 (\pm 0) | 9999 (\pm 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-related Quality of Life (HRQoL) as Assessed by EORTC-QLQ-C30 Score

| | |
|-----------------|---|
| End point title | Change From Baseline in Health-related Quality of Life (HRQoL) as Assessed by EORTC-QLQ-C30 Score |
|-----------------|---|

End point description:

EORTC QLQ-C30 scale uses 30 questions to assess participant functioning (physical, emotional, role, cognitive & social), symptoms (fatigue, nausea & vomiting, pain), global health/QoL & 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea & financial difficulties). Change in HRQoL was assessed using participant responses to questions regarding Global Health Status (Q29: GHS; How would you rate your overall health during the past week?) & QoL (Q30: QoL; How would you rate your overall quality of life during the past week?) were scored on a 7-point scale (1= Very poor to 7=Excellent). Using linear transformation, raw scores are standardized. Scores range from 0-100. Higher score=better outcome. ITT population was used for analysis. Number analyzed=number of participants with data available for analysis. n=number of participants with data available for analysis at specified timepoint. 9999=No participants were analyzed at this timepoints.

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

End point timeframe:

Baseline, Day 1 of Cycles 2 to 16 (Cycle length = 21 days); study discontinuation visit (up to 1 year); Follow-up approximately every 3 months until disease recurrence or progression (up to approximately 4.5 years)

| End point values | Placebo | Atezolizumab | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198 | 200 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (Cycle 1 Day 1) (n= 198, 200) | 66.92 (\pm 21.41) | 67.54 (\pm 20.79) | | |
| Change at Cycle 2 Day 1 (n= 192, 191) | 2.99 (\pm 20.32) | 0.09 (\pm 18.33) | | |
| Change at Cycle 3 Day 1 (n= 190, 187) | 4.87 (\pm 24.02) | 0.49 (\pm 17.35) | | |
| Change at Cycle 4 Day 1 (n=175, 180) | 6.05 (\pm 21.04) | 1.34 (\pm 17.33) | | |
| Change at Cycle 5 Day 1 (n= 170, 168) | 5.29 (\pm 22.80) | 1.19 (\pm 18.25) | | |
| Change at Cycle 6 Day 1 (n=168, 163) | 4.66 (\pm 23.81) | 3.17 (\pm 18.01) | | |
| Change at Cycle 7 Day 1 (n=161, 155) | 7.25 (\pm 21.71) | 4.09 (\pm 17.47) | | |
| Change at Cycle 8 Day 1 (n=155, 151) | 7.58 (\pm 21.48) | 4.25 (\pm 19.93) | | |
| Change at Cycle 9 Day 1 (n=152, 147) | 6.30 (\pm 23.20) | 3.00 (\pm 17.93) | | |
| Change at Cycle 10 Day 1 (n=149, 143) | 7.83 (\pm 22.29) | 3.85 (\pm 17.12) | | |
| Change at Cycle 11 Day 1 (n=146, 139) | 7.65 (\pm 21.21) | 2.64 (\pm 17.35) | | |
| Change at Cycle 12 Day 1 (n=145, 138) | 7.47 (\pm 22.52) | 2.60 (\pm 17.75) | | |

| | | | | |
|--|------------------|------------------|--|--|
| Change at Cycle 13 Day 1 (n=140, 136) | 8.45 (± 21.37) | 2.94 (± 18.41) | | |
| Change at Cycle 14 Day 1 (n=135, 128) | 6.91 (± 21.82) | 3.39 (± 17.04) | | |
| Change at Cycle 15 Day 1 (n=134, 125) | 7.21 (± 21.58) | 5.27 (± 18.13) | | |
| Change at Cycle 16 Day 1 (n=123, 117) | 6.30 (± 22.87) | 6.05 (± 17.83) | | |
| Change at Study Discontinuation (n=179, 177) | 3.86 (± 23.64) | 1.55 (± 18.41) | | |
| Change at Follow Up 1 (n=50, 50) | 1.50 (± 25.01) | -5.83 (± 25.32) | | |
| Change at Follow Up 2 (n=41, 44) | 4.67 (± 21.33) | -0.95 (± 21.73) | | |
| Change at Follow Up 3 (n=33, 33) | -1.77 (± 18.84) | 2.53 (± 18.57) | | |
| Change at Follow Up 4 (n=34, 28) | 0.74 (± 25.32) | 3.87 (± 22.51) | | |
| Change at Follow Up 5 (n=29, 21) | 3.16 (± 23.19) | 4.76 (± 23.36) | | |
| Change at Follow Up 6 (n=29, 18) | 6.32 (± 23.11) | 1.85 (± 17.28) | | |
| Change at Follow Up 7 (n=17, 13) | 2.45 (± 23.34) | -10.26 (± 23.11) | | |
| Change at Follow Up 8 (n=17, 11) | -8.33 (± 32.00) | 2.27 (± 11.84) | | |
| Change at Follow Up 9 (n=9, 9) | 3.70 (± 17.24) | -1.85 (± 12.34) | | |
| Change at Follow Up 10 (n=5, 8) | -15.00 (± 50.14) | 9.38 (± 9.38) | | |
| Change at Follow Up 11 (n=9, 4) | -4.63 (± 50.88) | -4.17 (± 19.84) | | |
| Change at Follow Up 12 (n=5, 4) | 20.00 (± 40.23) | -14.58 (± 20.83) | | |
| Change at Follow Up 13 (n=6, 3) | 11.11 (± 38.61) | -2.78 (± 12.73) | | |
| Change at Follow Up 14 (n=2, 1) | 8.33 (± 11.79) | -16.67 (± 0) | | |
| Change at Follow Up 15 (n=4, 0) | 14.58 (± 34.94) | 9999 (± 9999) | | |
| Change at Follow Up 16 (n=3, 0) | 2.78 (± 12.73) | 9999 (± 9999) | | |
| Change at Follow Up 17 (n=2, 0) | -8.33 (± 11.79) | 9999 (± 9999) | | |
| Change at Follow Up 18 (n=2, 0) | 8.33 (± 11.79) | 9999 (± 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Atezolizumab

| | |
|-----------------|--|
| End point title | Serum Concentration of Atezolizumab ^[1] |
|-----------------|--|

End point description:

Pharmacokinetic (PK)-evaluable population included all participants who received at least one dose of atezolizumab and provided at least one PK sample that was evaluable. Number analyzed is the number of participants with data available for analysis. n = number of participants with data available for analysis at the specified timepoint. Different participants may have contributed data for each timepoint. 99999 = Geometric Mean and Geometric Coefficient of Variation were not evaluable as samples were below lower limit of quantification (BLQ).

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

End point timeframe:

Predose and 0.5 hours post dose on Cycle 1 Day 1; Predose on Day 1 of Cycles 2, 4, 8, and 16 (Cycle length=21 days); study discontinuation visit (up to 1 year)

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: This endpoint was planned to analyze the results only for subjects in the Atezolizumab arm who received at least one dose of atezolizumab and provided at least one PK sample that was evaluable.

| End point values | Atezolizumab | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 194 | | | |
| Units: micrograms per milliliters (ug/mL) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Day 1: Predose (n=187) | 99999 (± 99999) | | | |
| Cycle 1 Day 1: 0.5 hours Post-dose (n=183) | 447 (± 27.1) | | | |
| Cycle 2 Day 1: Predose (n=191) | 99.2 (± 31.1) | | | |
| Cycle 4 Day 1: Predose (n=174) | 186 (± 64.3) | | | |
| Cycle 8 Day 1: Predose (n=137) | 238 (± 40.6) | | | |
| Cycle 16 Day 1: Predose (n=113) | 257 (± 40.3) | | | |
| Study Discontinuation (n=170) | 178 (± 141.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with at Least One Adverse Event (AE)

| | |
|-----------------|---|
| End point title | Number of Participants with at Least One Adverse Event (AE) |
|-----------------|---|

End point description:

An AE is untoward medical occurrence in participant administered a pharmaceutical product & regardless of causal relationship with this treatment. An AE can therefore be any unfavorable & unintended sign (including an abnormal laboratory finding), symptom/disease temporally associated with use of investigational product, whether or not considered related to investigational product. Safety evaluable population included all randomized participants who received any amount of the study treatment.

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

End point timeframe:

From first dose of study drug until 90 days after the last dose of study drug (up to 1 year, 3 months)

| End point values | Placebo | Atezolizumab | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 | 202 | | |
| Units: participants | 186 | 192 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-Drug Antibodies (ADA) to Atezolizumab

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

End point description:

Number of participants positive for Treatment Emergent ADA is the number of post-baseline evaluable participants determined to have treatment induced ADA or treatment-enhanced ADA during the study period. ADA evaluable population included all randomized participants who received at least one dose of atezolizumab and who had at least one post-baseline ADA result.

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

End point timeframe:

Predose on Day 1 of Cycles 1, 2, 4, 8 and 16 (Cycle length=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: This endpoint was planned to analyze the results only for subjects in the Atezolizumab arm who received at least one dose of atezolizumab and who had at least one post-baseline ADA result.

| End point values | Atezolizumab | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 192 | | | |
| Units: participants | 13 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For adverse events (AEs): From first dose of study drug until 90 days after the last dose of study drug (up to 1 year, 3 months); For all-cause mortality: from randomization through the end of post-treatment survival follow-up (up to 5 years, 5 months)

Adverse event reporting additional description:

Safety-evaluable population included all randomized participants who received any amount of the study treatment.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 26.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Atezolizumab 1200 mg |
|-----------------------|----------------------|

Reporting group description:

Participants received atezolizumab 1200 mg, IV infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first.

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

Reporting group description:

Participants received atezolizumab matching placebo, IV infusion on Day 1 of each 21-day cycle for 16 cycles or up to 1 year or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by sponsor, whichever occurred first.

| Serious adverse events | Atezolizumab 1200 mg | Placebo | |
|---|----------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 32 / 202 (15.84%) | 32 / 203 (15.76%) | |
| number of deaths (all causes) | 70 | 69 | |
| number of deaths resulting from adverse events | 3 | 5 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal adenoma | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Gastrostomy | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle flap operation | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medical device removal | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fistula repair | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 2 / 202 (0.99%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 1 | |
| Implant site pain | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Stridor | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal necrosis | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal haemorrhage | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal stenosis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal oedema | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Mental disorder | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (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 / 202 (0.50%) | 0 / 203 (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 / 202 (0.50%) | 0 / 203 (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 | | | |
| Anastomotic stenosis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoradionecrosis | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative adhesion | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation necrosis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 202 (0.99%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salivary gland fistula | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toothache | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Lichen planus | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (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 | | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prerenal failure | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Soft tissue necrosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (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 | | | |
| Medical device site infection | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epiglottitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine infection | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericoronitis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngolaryngeal abscess | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 6 / 202 (2.97%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Atezolizumab 1200 mg | Placebo | |
|---|----------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 155 / 202 (76.73%) | 144 / 203 (70.94%) | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 12 / 202 (5.94%) | 6 / 203 (2.96%) | |
| occurrences (all) | 14 | 10 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 13 / 202 (6.44%) | 5 / 203 (2.46%) | |
| occurrences (all) | 17 | 8 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 11 / 202 (5.45%) | 7 / 203 (3.45%) | |
| occurrences (all) | 16 | 7 | |
| Weight decreased | | | |
| subjects affected / exposed | 13 / 202 (6.44%) | 11 / 203 (5.42%) | |
| occurrences (all) | 15 | 11 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 14 / 202 (6.93%) | 11 / 203 (5.42%) | |
| occurrences (all) | 22 | 11 | |

| | | | |
|--|-----------------------------|-------------------|-------------------|
| Blood and lymphatic system disorders | | | |
| | Lymphopenia | | |
| | subjects affected / exposed | 8 / 202 (3.96%) | 22 / 203 (10.84%) |
| | occurrences (all) | 11 | 36 |
| | Anaemia | | |
| | subjects affected / exposed | 19 / 202 (9.41%) | 18 / 203 (8.87%) |
| | occurrences (all) | 24 | 21 |
| General disorders and administration site conditions | | | |
| | Fatigue | | |
| | subjects affected / exposed | 29 / 202 (14.36%) | 26 / 203 (12.81%) |
| | occurrences (all) | 32 | 30 |
| | Asthenia | | |
| | subjects affected / exposed | 11 / 202 (5.45%) | 16 / 203 (7.88%) |
| | occurrences (all) | 20 | 22 |
| Gastrointestinal disorders | | | |
| | Constipation | | |
| | subjects affected / exposed | 12 / 202 (5.94%) | 5 / 203 (2.46%) |
| | occurrences (all) | 13 | 5 |
| | Diarrhoea | | |
| | subjects affected / exposed | 26 / 202 (12.87%) | 10 / 203 (4.93%) |
| | occurrences (all) | 40 | 10 |
| | Dry mouth | | |
| | subjects affected / exposed | 18 / 202 (8.91%) | 16 / 203 (7.88%) |
| | occurrences (all) | 21 | 16 |
| Respiratory, thoracic and mediastinal disorders | | | |
| | Cough | | |
| | subjects affected / exposed | 17 / 202 (8.42%) | 12 / 203 (5.91%) |
| | occurrences (all) | 21 | 12 |
| | Oropharyngeal pain | | |
| | subjects affected / exposed | 6 / 202 (2.97%) | 11 / 203 (5.42%) |
| | occurrences (all) | 7 | 15 |
| Skin and subcutaneous tissue disorders | | | |
| | Pruritus | | |
| | subjects affected / exposed | 23 / 202 (11.39%) | 15 / 203 (7.39%) |
| | occurrences (all) | 27 | 17 |
| | Rash | | |
| | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 13 / 202 (6.44%) 25 | 17 / 203 (8.37%) 18 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 12 / 202 (5.94%) 15 | 5 / 203 (2.46%) 5 | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) Hyperthyroidism subjects affected / exposed occurrences (all) | 54 / 202 (26.73%) 59 11 / 202 (5.45%) 11 | 34 / 203 (16.75%) 36 1 / 203 (0.49%) 1 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) | 22 / 202 (10.89%) 27 12 / 202 (5.94%) 13 | 16 / 203 (7.88%) 22 5 / 203 (2.46%) 5 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all) | 16 / 202 (7.92%) 17 6 / 202 (2.97%) 9 | 16 / 203 (7.88%) 16 12 / 203 (5.91%) 17 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 03 November 2017 | <ol style="list-style-type: none">1. Revision of EFS definition2. Interim OS analysis added to previously planned EFS interim analysis, with related changes to sample size determination3. Sensitivity analyses of EFS added to assess impacts of missing data, new anti-cancer therapy, loss to follow-up, discontinuation |
| 21 February 2018 | Voluntary Harmonisation Procedure and related changes, including: rationale to support treatment duration (16 cycles or up to 1 year), reduce risk of overlapping toxicities (28 days or 5 half-lives between investigational medicinal products [IMPs]), optional interim analyses removed. |
| 01 April 2018 | <ol style="list-style-type: none">1. Removal of screening pelvis computer tomography (CT) or magnetic resonance imaging (MRI)2. Addition of chest CT or MRI at every tumor assessment3. Addition of contrast requirement for CT or MRI of head and neck, as well as chest and abdomen, with specified exceptions |
| 15 June 2018 | <ol style="list-style-type: none">1. Revised timing of surgery for removal of residual disease, initiation of study treatment, and subsequent assessments2. Additional exclusion criteria: patients who received unapproved anti-estimated glomerular filtration rate (EGFR) agents or unapproved radiotherapy, patients with current second primary SCCHN, patients who received surgery alone or radiotherapy alone3. Testing of total carbon dioxide permitted in place of bicarbonate4. Requirement for testing of hepatitis B virus (HBV) surface antibody removed, hepatitis B surface antigen (HBsAg) and total Hepatitis B core antibody (HBcAb) tested instead5. Additional safety monitoring for special situations including accidental overdose and medication error6. Voluntary Harmonisation Procedure and further related changes, including clarification of tissue sample submission after randomization |
| 10 October 2018 | <ol style="list-style-type: none">1. Clarification of eligibility assessment involving clinical staging, with tumor staging and nodal staging to be assessed synchronously2. Restructuring of inclusion criteria pertaining to prior definitive local therapy, confirmed response to prior local therapy, and absence of metastatic disease3. Inclusion criteria were modified to allow participation of participants who undergo salvage laryngectomy, to require female contraception and abstaining from egg donation4. Exclusion criteria were modified to exclude HPV negative participants with TX or NX or Tis, HPV positive participants with T0 or NX, participants with squamous cell carcinoma of the paranasal sinus or any carcinoma of non-squamous histology, participants who underwent prior systemic adjuvant therapy5. Collection of patient reported outcomes (PROs) was modified to allow telephone assessment, the Quality-of-Life-Head and Neck, Module 35 Questionnaire (QLQ-H & N35) was modified to omit additional questions related to swallowing6. Guidelines for management of AEs related to atezolizumab were revised to include nephritis7. Clarification on treatment interruption/withholding and resumption |
| 16 December 2019 | <ol style="list-style-type: none">1. Additional approved indications for atezolizumab included in background2. Systemic immune activation replaced with hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS)3. Atezolizumab risks and AE management guidelines updated to include myositis, HLH, and MAS; to allow longer treatment interruption and resumption of study treatment; to add laboratory testing and cardiac imaging related to myocarditis |

| | |
|------------------|---|
| 07 January 2021 | <ol style="list-style-type: none"> Investigator-assessed EFS added as primary endpoint IRF-assessed EFS changed to secondary endpoint Efficacy boundaries for the second interim and final OS analyses were modified China extension cohort added to achieve adequate sample size for cohort-specific analysis of efficacy and safety Immunosuppressive therapy removed from prohibited therapy and added to cautionary therapy to allow for use in immune-mediated adverse events Identified risks and adverse events of special interest (AESIs) associated with atezolizumab were updated AE management guidelines for infusion-related reactions, dermatologic reactions, myositis, cytokine release syndrome (CRS), HLH, and MAS were updated. Pregnancy monitoring and investigator notification language was added |
| 22 October 2021 | <ol style="list-style-type: none"> Alignment with clinical trials regulation guidelines OS changed from co-primary endpoint to key secondary endpoint to be tested if INV-EFS is positive |
| 04 November 2021 | Investigator-assessed and IRF EFS assessments at 3 and 4-year landmarks added |
| 24 February 2023 | <ol style="list-style-type: none"> OS assessment at 5-year landmark added, 1-year landmark removed PRO assessments during follow up reduced to decrease participant burden China extension cohort removed Changed study assumptions about expected outcomes for participants with Stage III and IV SCCHN, including EFS and OS COVID-19 benefit-risk assessment added Futility assessment of EFS added Atezolizumab AE management guidelines updated Updated list of preexisting autoimmune disease and immune deficiencies excluding participants from study participation HLH and MAS replaced systemic inflammatory response syndrome on list of atezolizumab-associated AESIs |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---------------|--|--------------|
| 06 March 2024 | The decision to terminate the study as its primary endpoint of INV-EFS was not met at its final EFS analysis. No new safety signals were identified. | - |

Notes:

Limitations and caveats

None reported