# Clinical trial results:
# A Phase I/III, Randomized, Double-Blind, Placebo-Controlled Study of Carboplatin Plus Etoposide With or Without Atezolizumab (Anti-PD-L1 Antibody) in Patients With Untreated Extensive-Stage Small Cell Lung Cancer

## Summary

| | |
|---|---|
| EudraCT number | 2015-004861-97 |
| Trial protocol | DE PL HU CZ GB AT GR ES FR IT |
| Global end of trial date | |

**Results information**

| | |
|---|---|
| Result version number | v2 |
| This version publication date | 06 June 2019 |
| First version publication date | 05 May 2019 |
| Version creation reason | |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | GO30081 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02763579 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Interim |
| Date of interim/final analysis | 24 April 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 April 2018 |
| Global end of trial reached? | No |

Notes:

## General information about the trial

Main objective of the trial:

This randomized, Phase I/III, multicenter, double-blinded, placebo-controlled study was designed to evaluate the safety and efficacy of atezolizumab (anti-programmed death-ligand 1 [PD-L1] antibody) in combination with carboplatin plus (+) etoposide compared with treatment with placebo + carboplatin + etoposide in subjects with chemotherapy-naive extensive-stage small cell lung cancer.

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 | 07 June 2016 |
| 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: 11 |
| Country: Number of subjects enrolled | China: 1 |
| Country: Number of subjects enrolled | Japan: 42 |
| Country: Number of subjects enrolled | Korea, Republic of: 17 |
| Country: Number of subjects enrolled | Taiwan: 9 |
| Country: Number of subjects enrolled | Austria: 20 |
| Country: Number of subjects enrolled | Czech Republic: 17 |
| Country: Number of subjects enrolled | Germany: 9 |
| Country: Number of subjects enrolled | Spain: 25 |
| Country: Number of subjects enrolled | France: 7 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Mexico: 4 |
| Country: Number of subjects enrolled | United States: 86 |
| Country: Number of subjects enrolled | Brazil: 4 |
| Country: Number of subjects enrolled | Chile: 6 |
| Country: Number of subjects enrolled | Greece: 11 |
| Country: Number of subjects enrolled | Hungary: 19 |
| Country: Number of subjects enrolled | Italy: 15 |
| Country: Number of subjects enrolled | Poland: 45 |
| Country: Number of subjects enrolled | Russian Federation: 30 |
| Country: Number of subjects enrolled | Serbia: 15 |

| | |
|---|---|
| Worldwide total number of subjects | 403 |
| EEA total number of subjects | 178 |

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) | 217 |
| From 65 to 84 years | 184 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Subjects in this study included: extensive-stage small cell lung cancer (ES-SCLC) with no prior systemic treatment for ES-SCLC.

### 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 + Carboplatin + Etoposide |

Arm description:

Subjects received intravenous infusions of atezolizumab 1200 milligrams (mg) in combination with carboplatin to achieve an initial target area under the concentration-time curve (AUC) of 5 milligrams per milliliter per minute (mg/mL/min) followed by etoposide 100 milligrams per square meter (mg/m^2) on Day 1 of every 21-day cycle during the induction phase (Cycles 1-4). On Days 2 and 3 of every 21-day cycle during the induction phase (Cycles 1-4), etoposide 100 mg/m^2 was administered alone. Thereafter, subjects received maintenance (Cycle 5 onward) atezolizumab 1200 mg on Day 1 of every 21-day cycle until persistent radiographic PD, symptomatic deterioration, intolerable toxicity, withdrawal of consent, death, or study termination by the Sponsor.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Atezolizumab |
| Investigational medicinal product code | |
| Other name | MPDL3280A, Tecentriq |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Atezolizumab intravenous infusion was administered at a dose of 1200 mg on Day 1 of each 21-day cycle during the induction phase (Cycles 1-4) and maintenance phase (Cycle 5 onward).

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

Dosage and administration details:

Carboplatin intravenous infusion to achieve an initial target AUC of 5 mg/mL/min was administered on Day 1 of each 21-day cycle during the induction phase (Cycles 1-4).

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

Dosage and administration details:

Etoposide intravenous infusion was administered at a dose of 100 mg/m^2 on Days 1, 2, and 3 of each 21-day cycle during the induction phase (Cycles 1-4).

| | |
|---|---|
| **Arm title** | Placebo + Carboplatin + Etoposide |

Arm description:

Subjects received intravenous infusions of placebo in combination with carboplatin to achieve an initial target AUC of 5 mg/mL/min followed by etoposide 100 mg/m^2 on Day 1 of every 21-day cycle during the induction phase (Cycles 1-4). On Days 2 and 3 of every 21-day cycle during the induction phase (Cycles 1-4), etoposide 100 mg/m^2 was administered alone. Thereafter, subjects received maintenance (Cycle 5 onward) placebo on Day 1 of every 21-day cycle until persistent radiographic PD, symptomatic deterioration, intolerable toxicity, withdrawal of consent, death, or study termination by the Sponsor.

| | |
|---|---|
| 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:

Placebo intravenous infusion was administered on Day 1 of each 21-day cycle during the induction phase (Cycles 1-4) and maintenance phase (Cycle 5 onward).

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

Dosage and administration details:

Carboplatin intravenous infusion to achieve an initial target AUC of 5 mg/mL/min was administered on Day 1 of each 21-day cycle during the induction phase (Cycles 1-4).

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

Dosage and administration details:

Etoposide intravenous infusion was administered at a dose of 100 mg/m^2 on Days 1, 2, and 3 of each 21-day cycle during the induction phase (Cycles 1-4).

| **Number of subjects in period 1** | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide |
|---|---|---|
| Started | 201 | 202 |
| Completed | 0 | 0 |
| Not completed | 201 | 202 |
| Adverse event, serious fatal | 101 | 132 |
| Consent withdrawn by subject | 18 | 9 |
| Physician decision | 2 | - |
| On-going in study | 77 | 60 |
| Lost to follow-up | 3 | 1 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Atezolizumab + Carboplatin + Etoposide |
|---|---|

Reporting group description:

Subjects received intravenous infusions of atezolizumab 1200 milligrams (mg) in combination with carboplatin to achieve an initial target area under the concentration-time curve (AUC) of 5 milligrams per milliliter per minute (mg/mL/min) followed by etoposide 100 milligrams per square meter (mg/m^2) on Day 1 of every 21-day cycle during the induction phase (Cycles 1-4). On Days 2 and 3 of every 21-day cycle during the induction phase (Cycles 1-4), etoposide 100 mg/m^2 was administered alone. Thereafter, subjects received maintenance (Cycle 5 onward) atezolizumab 1200 mg on Day 1 of every 21-day cycle until persistent radiographic PD, symptomatic deterioration, intolerable toxicity, withdrawal of consent, death, or study termination by the Sponsor.

| Reporting group title | Placebo + Carboplatin + Etoposide |
|---|---|

Reporting group description:

Subjects received intravenous infusions of placebo in combination with carboplatin to achieve an initial target AUC of 5 mg/mL/min followed by etoposide 100 mg/m^2 on Day 1 of every 21-day cycle during the induction phase (Cycles 1-4). On Days 2 and 3 of every 21-day cycle during the induction phase (Cycles 1-4), etoposide 100 mg/m^2 was administered alone. Thereafter, subjects received maintenance (Cycle 5 onward) placebo on Day 1 of every 21-day cycle until persistent radiographic PD, symptomatic deterioration, intolerable toxicity, withdrawal of consent, death, or study termination by the Sponsor.

| **Reporting group values** | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | Total |
|---|---|---|---|
| Number of subjects | 201 | 202 | 403 |
| 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) | 111 | 106 | 217 |
| From 65-84 years | 89 | 95 | 184 |
| 85 years and over | 1 | 1 | 2 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 63.8 | 63.6 | |
| standard deviation | ± 8.8 | ± 9.0 | - |
| Gender categorical | | | |
| As reported from Electronic Case Report Form (eCRF). | | | |
| Units: Subjects | | | |
| Female | 72 | 70 | 142 |
| Male | 129 | 132 | 261 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Atezolizumab + Carboplatin + Etoposide |

Reporting group description:

Subjects received intravenous infusions of atezolizumab 1200 milligrams (mg) in combination with carboplatin to achieve an initial target area under the concentration-time curve (AUC) of 5 milligrams per milliliter per minute (mg/mL/min) followed by etoposide 100 milligrams per square meter (mg/m^2) on Day 1 of every 21-day cycle during the induction phase (Cycles 1-4). On Days 2 and 3 of every 21-day cycle during the induction phase (Cycles 1-4), etoposide 100 mg/m^2 was administered alone. Thereafter, subjects received maintenance (Cycle 5 onward) atezolizumab 1200 mg on Day 1 of every 21-day cycle until persistent radiographic PD, symptomatic deterioration, intolerable toxicity, withdrawal of consent, death, or study termination by the Sponsor.

| | |
|---|---|
| Reporting group title | Placebo + Carboplatin + Etoposide |

Reporting group description:

Subjects received intravenous infusions of placebo in combination with carboplatin to achieve an initial target AUC of 5 mg/mL/min followed by etoposide 100 mg/m^2 on Day 1 of every 21-day cycle during the induction phase (Cycles 1-4). On Days 2 and 3 of every 21-day cycle during the induction phase (Cycles 1-4), etoposide 100 mg/m^2 was administered alone. Thereafter, subjects received maintenance (Cycle 5 onward) placebo on Day 1 of every 21-day cycle until persistent radiographic PD, symptomatic deterioration, intolerable toxicity, withdrawal of consent, death, or study termination by the Sponsor.

### Primary: Duration of Progression-Free Survival (PFS) as Assessed by the Investigator Using RECIST v1.1

| | |
|---|---|
| End point title | Duration of Progression-Free Survival (PFS) as Assessed by the Investigator Using RECIST v1.1 |

End point description:

Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0), as at least 20% increase in the sum of the longest diameter of target lesions compared to baseline, or unequivocal progression in non-target lesion(s), or the appearance of new lesion(s).

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

End point timeframe:

Baseline until PD or death, whichever occurs first (up to approximately 23 months)

| End point values | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 201 | 202 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 5.2 (4.4 to 5.6) | 4.3 (4.2 to 4.5) | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis for PFS |
|---|---|
| Comparison groups | Atezolizumab + Carboplatin + Etoposide v Placebo + Carboplatin + Etoposide |

| | |
|---|---|
| Number of subjects included in analysis | 403 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.017 |
| Method | Logrank |
| Parameter estimate | Stratified Hazard Ratio |
| Point estimate | 0.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 0.96 |

## Primary: Duration of Overall Survival (OS)

| | |
|---|---|
| End point title | Duration of Overall Survival (OS) |

End point description:

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

End point timeframe:

Baseline until death from any cause (up to approximately 23 months)

| End point values | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 201 | 202 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 12.3 (10.8 to 15.9) | 10.3 (9.3 to 11.3) | | |

## Statistical analyses

| Statistical analysis title | Statistical Analysis for OS |
|---|---|
| Comparison groups | Atezolizumab + Carboplatin + Etoposide v Placebo + Carboplatin + Etoposide |
| Number of subjects included in analysis | 403 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0069 |
| Method | Logrank |
| Parameter estimate | Stratified Hazard Ratio |
| Point estimate | 0.7 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.91 |

## Secondary: Percentage of Participants With Objective Response (OR) as Assessed by the Investigator Using RECIST v1.1

| End point title | Percentage of Participants With Objective Response (OR) as Assessed by the Investigator Using RECIST v1.1 |
|---|---|

End point description:

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

End point timeframe:

Baseline until partial response (PR) or complete response (CR), whichever occurs first (up to approximately 46 months)

| **End point values** | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[1] | 0[2] | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | ( to ) | ( to ) | | |

Notes:

[1] - Data will be analyzed at the time of study completion.

[2] - Data will be analyzed at the time of study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response (DOR) as Assessed by the Investigator Using RECIST v1.1

| End point title | Duration of Response (DOR) as Assessed by the Investigator Using RECIST v1.1 |
|---|---|

End point description:

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

End point timeframe:

First occurrence of PR or CR until PD or death, whichever occurs first (up to approximately 46 months)

| End point values | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[3] | 0[4] | | |
| Units: Months | | | | |
| median (standard deviation) | () | () | | |

Notes:

[3] - Data will be analyzed at the time of study completion.

[4] - Data will be analyzed at the time of study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Alive and Without PD, as Assessed by the Investigator Using RECIST v1.1, at 6 Months and 1 Year

| End point title | Percentage of Participants Alive and Without PD, as Assessed by the Investigator Using RECIST v1.1, at 6 Months and 1 Year |
|---|---|

End point description:

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

End point timeframe:

6 months, 1 year (up to approximately 46 months)

| End point values | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[5] | 0[6] | | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |

Notes:

[5] - Data will be analyzed at the time of study completion.

[6] - Data will be analyzed at the time of study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Alive at 1 Year and 2 Years

| End point title | Percentage of Participants Alive at 1 Year and 2 Years |
|---|---|

End point description:

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

End point timeframe:

1 year, 2 years (up to approximately 46 months)

| End point values | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[7] | 0[8] | | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |

Notes:

[7] - Data will be analyzed at the time of study completion.

[8] - Data will be analyzed at the time of study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Deterioration (TTD) per European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 (C30) Score

| End point title | Time to Deterioration (TTD) per European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 (C30) Score |
|---|---|

End point description:

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

End point timeframe:

Baseline until deterioration per symptom subscale (up to approximately 46 months)

| End point values | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[9] | 0[10] | | |
| Units: Month | | | | |
| median (confidence interval 95%) | ( to ) | ( to ) | | |

Notes:

[9] - Data will be analyzed at the time of study completion.

[10] - Data will be analyzed at the time of study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: TTD per EORTC QLQ Lung Cancer Module (LC13) Score

| End point title | TTD per EORTC QLQ Lung Cancer Module (LC13) Score |
|---|---|

End point description:

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

End point timeframe:

Baseline until deterioration per symptom subscale (up to approximately 46 months)

| End point values | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[11] | 0[12] | | |
| Units: Month | | | | |
| median (confidence interval 95%) | ( to ) | ( to ) | | |

Notes:

[11] - Data will be analyzed at the time of study completion.

[12] - Data will be analyzed at the time of study completion.

### 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:

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

End point timeframe:

Baseline until up to 90 days after end of treatment (up to approximately 46 months)

| End point values | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[13] | 0[14] | | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |

Notes:

[13] - Data will be analyzed at the time of study completion.

[14] - Data will be analyzed at the time of study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Anti-Therapeutic Antibodies (ATAs)

| End point title | Percentage of Participants With Anti-Therapeutic Antibodies (ATAs) |
|---|---|

End point description:

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

End point timeframe:

Predose (0 hours [H]) on Day (D) 1 of Cycles (C) 1, 2, 3, 4, 8, 16, and every 8 cycles (Q8C) thereafter (cycle = 21 days) until treatment discontinuation (up to 46 months) and 120 days after last dose (up to

| End point values | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[15] | 0[16] | | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |

Notes:

[15] - Data will be analyzed at the time of study completion.

[16] - Data will be analyzed at the time of study completion.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Observed Serum Concentration (Cmax) of Atezolizumab

| End point title | Maximum Observed Serum Concentration (Cmax) of Atezolizumab |
|---|---|

End point description:

Atezolizumab infusion duration is 60 minutes for the first infusion and 30 minutes for subsequent infusions.

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

End point timeframe:

Predose (0 H) and postdose (0.5 H) on D1 of C1; predose (0 H) on D1 of C2, 3, 4, 8, 16, and Q8C thereafter (cycle = 21 days) until treatment discontinuation (up to 46 months) and 120 days after last dose (up to approximately 46 months overall)

| End point values | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[17] | 0[18] | | |
| Units: mcg/mL | | | | |
| geometric mean (standard deviation) | () | () | | |

Notes:

[17] - Data will be analyzed at the time of study completion.

[18] - Data will be analyzed at the time of study completion.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Minimum Observed Serum Concentration (Cmin) of Atezolizumab

| End point title | Minimum Observed Serum Concentration (Cmin) of Atezolizumab |
|---|---|

End point description:

Atezolizumab infusion duration is 60 minutes for the first infusion and 30 minutes for subsequent

infusions.

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

End point timeframe:

Predose (0 H) on D1 of C1, 2, 3, 4, 8, 16, and Q8C thereafter (cycle = 21 days) until treatment discontinuation (up to 46 months) and 120 days after last dose (up to approximately 46 months overall)

| **End point values** | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[19] | 0[20] | | |
| Units: mcg/mL | | | | |
| geometric mean (standard deviation) | () | () | | |

Notes:

[19] - Data will be analyzed at the time of study completion.

[20] - Data will be analyzed at the time of study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Concentration of Carboplatin

| End point title | Plasma Concentration of Carboplatin |
|---|---|

End point description:

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

End point timeframe:

Predose (0 H) and 5-10 minutes before end/1 H after end of carboplatin infusion (infusion duration = 1 H) on D1 of C1 and C3 (cycle = 21 days)(up to approximately 46 months)

| **End point values** | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[21] | 0[22] | | |
| Units: mcg/mL | | | | |
| geometric mean (standard deviation) | () | () | | |

Notes:

[21] - Data will be analyzed at the time of study completion.

[22] - Data will be analyzed at the time of study completion.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Concentration of Etoposide

| End point title | Plasma Concentration of Etoposide |
|---|---|

End point description:

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

End point timeframe:

Predose (0 H) and 5-10 minutes before end/1 H and 4H after end of etoposide infusion (infusion duration = 1 H) on D1 of C1 and C3 (cycle = 21 days)(up to approximately 46 months)

| **End point values** | Atezolizumab + Carboplatin + Etoposide | Placebo + Carboplatin + Etoposide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[23] | 0[24] | | |
| Units: mcg/mL | | | | |
| geometric mean (standard deviation) | () | () | | |

Notes:

[23] - Data will be analyzed at the time of study completion.

[24] - Data will be analyzed at the time of study completion.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first study drug administration to the data cutoff date: 24 April 2018 (up to 23 months).

Adverse event reporting additional description:

Adverse Events reporting is for the Safety Evaluable Participants. Safety Evaluable Participants is defined as patients who received any amount of any component of study treatment.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

### Reporting groups

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| Reporting group title | Placebo + Carboplatin + Etoposide |

Reporting group description:

Subjects received intravenous infusions of placebo in combination with carboplatin to achieve an initial target AUC of 5 mg/mL/min followed by etoposide 100 mg/m^2 on Day 1 of every 21-day cycle during the induction phase (Cycles 1-4). On Days 2 and 3 of every 21-day cycle during the induction phase (Cycles 1-4), etoposide 100 mg/m^2 was administered alone. Thereafter, subjects received maintenance (Cycle 5 onward) placebo on Day 1 of every 21-day cycle until persistent radiographic PD, symptomatic deterioration, intolerable toxicity, withdrawal of consent, death, or study termination by the Sponsor.

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|---|---|
| Reporting group title | Atezolizumab + Carboplatin + Etoposide |

Reporting group description:

Subjects received intravenous infusions of atezolizumab 1200 milligrams (mg) in combination with carboplatin to achieve an initial target area under the concentration-time curve (AUC) of 5 milligrams per milliliter per minute (mg/mL/min) followed by etoposide 100 milligrams per square meter (mg/m^2) on Day 1 of every 21-day cycle during the induction phase (Cycles 1-4). On Days 2 and 3 of every 21-day cycle during the induction phase (Cycles 1-4), etoposide 100 mg/m^2 was administered alone. Thereafter, subjects received maintenance (Cycle 5 onward) atezolizumab 1200 mg on Day 1 of every 21-day cycle until persistent radiographic PD, symptomatic deterioration, intolerable toxicity, withdrawal of consent, death, or study termination by the Sponsor.

| **Serious adverse events** | Placebo + Carboplatin + Etoposide | Atezolizumab + Carboplatin + Etoposide | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 68 / 196 (34.69%) | 74 / 198 (37.37%) | |
| number of deaths (all causes) | 130 | 103 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| METASTATIC NEOPLASM | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TUMOUR PAIN | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| PERIPHERAL ARTERIAL OCCLUSIVE DISEASE | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERIPHERAL ARTERY OCCLUSION | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUPERIOR VENA CAVA SYNDROME | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THROMBOPHLEBITIS | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| 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 | 1 / 196 (0.51%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHEST PAIN | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEATH | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |

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|---|---|---|---|
| FATIGUE | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 3 / 198 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| NON−CARDIAC CHEST PAIN | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYREXIA | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SYSTEMIC INFLAMMATORY RESPONSE SYNDROME | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (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 | | | |
| ACUTE RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| BRONCHIAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 196 (1.02%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMOPTYSIS | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| HYPERCAPNIA | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONITIS | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY OEDEMA | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| ALCOHOL ABUSE | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEPRESSION | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BLOOD ALKALINE PHOSPHATASE INCREASED | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BLOOD CREATININE INCREASED | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LIVER FUNCTION TEST INCREASED | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLATELET COUNT DECREASED | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TRANSAMINASES INCREASED | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| WHITE BLOOD CELL COUNT DECREASED | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (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 | | | |
| FEMUR FRACTURE | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEAD INJURY | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFUSION RELATED REACTION | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RADIATION OESOPHAGITIS | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THORACIC VERTEBRAL FRACTURE | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATRIOVENTRICULAR BLOCK COMPLETE | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC TAMPONADE | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIOPULMONARY FAILURE | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| PERICARDIAL EFFUSION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| SUPRAVENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| CEREBROVASCULAR ACCIDENT | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GUILLAIN−BARRE SYNDROME | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SOMNOLENCE | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SYNCOPE | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 3 / 198 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL CORD OEDEMA | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TRANSIENT ISCHAEMIC ATTACK | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TRIGEMINAL NEURALGIA | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Blood and lymphatic system disorders** | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 3 / 198 (1.52%) | |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DISSEMINATED INTRAVASCULAR COAGULATION | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed | 9 / 196 (4.59%) | 5 / 198 (2.53%) | |
| occurrences causally related to treatment / all | 9 / 9 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LEUKOCYTOSIS | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 8 / 196 (4.08%) | 7 / 198 (3.54%) | |
| occurrences causally related to treatment / all | 8 / 8 | 7 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| PANCYTOPENIA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 196 (2.04%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 4 / 196 (2.04%) | 5 / 198 (2.53%) | |
| occurrences causally related to treatment / all | 4 / 4 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL ADHESIONS | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NAUSEA | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LIP OEDEMA | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ILEUS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRITIS | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FAECES DISCOLOURED | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRIC ULCER PERFORATION | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIVERTICULAR PERFORATION | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 3 / 198 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COLITIS | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCREATITIS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCREATITIS ACUTE | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PROCTITIS | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| AUTOIMMUNE COLITIS | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VOMITING | | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 3 / 198 (1.52%) | |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| CHOLANGITIS | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| JAUNDICE | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| RASH | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SKIN TOXICITY | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TUBULOINTERSTITIAL NEPHRITIS | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| AUTOIMMUNE THYROIDITIS | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (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 | | | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| BRONCHITIS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CLOSTRIDIUM DIFFICILE COLITIS | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CLOSTRIDIUM DIFFICILE INFECTION | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CYTOMEGALOVIRUS INFECTION | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUNG ABSCESS | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUNG INFECTION | | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIC SEPSIS | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 7 / 196 (3.57%) | 9 / 198 (4.55%) | |
| occurrences causally related to treatment / all | 1 / 8 | 4 / 12 | |
| deaths causally related to treatment / all | 1 / 3 | 1 / 1 | |
| PULMONARY SEPSIS | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| PYOPNEUMOTHORAX | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPSIS | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| SEPTIC SHOCK | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (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 | 2 / 196 (1.02%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| DEHYDRATION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 198 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOMAGNESAEMIA | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 4 / 196 (2.04%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo + Carboplatin + Etoposide | Atezolizumab + Carboplatin + Etoposide | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 186 / 196 (94.90%) | 190 / 198 (95.96%) | |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 6 / 196 (3.06%) | 15 / 198 (7.58%) | |
| occurrences (all) | 8 | 20 | |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 19 / 196 (9.69%) | 23 / 198 (11.62%) | |
| occurrences (all) | 25 | 27 | |
| CHEST PAIN | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 12 / 196 (6.12%) | 16 / 198 (8.08%) | |
| occurrences (all) | 12 | 19 | |
| FATIGUE | | | |
| subjects affected / exposed | 49 / 196 (25.00%) | 51 / 198 (25.76%) | |
| occurrences (all) | 61 | 65 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 7 / 196 (3.57%) | 13 / 198 (6.57%) | |
| occurrences (all) | 8 | 14 | |
| PYREXIA | | | |
| subjects affected / exposed | 16 / 196 (8.16%) | 18 / 198 (9.09%) | |
| occurrences (all) | 18 | 29 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 25 / 196 (12.76%) | 18 / 198 (9.09%) | |
| occurrences (all) | 29 | 22 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 16 / 196 (8.16%) | 19 / 198 (9.60%) | |
| occurrences (all) | 17 | 22 | |
| HAEMOPTYSIS | | | |
| subjects affected / exposed | 10 / 196 (5.10%) | 14 / 198 (7.07%) | |
| occurrences (all) | 10 | 20 | |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed | 5 / 196 (2.55%) | 12 / 198 (6.06%) | |
| occurrences (all) | 6 | 15 | |
| PRODUCTIVE COUGH | | | |
| subjects affected / exposed | 9 / 196 (4.59%) | 10 / 198 (5.05%) | |
| occurrences (all) | 14 | 10 | |
| Psychiatric disorders | | | |
| INSOMNIA | | | |
| subjects affected / exposed | 13 / 196 (6.63%) | 15 / 198 (7.58%) | |
| occurrences (all) | 13 | 18 | |
| Investigations | | | |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed | 45 / 196 (22.96%) | 37 / 198 (18.69%) | |
| occurrences (all) | 80 | 74 | |
| PLATELET COUNT DECREASED | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 28 / 196 (14.29%) | 25 / 198 (12.63%) | |
| occurrences (all) | 39 | 36 | |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 10 / 196 (5.10%) | 20 / 198 (10.10%) | |
| occurrences (all) | 11 | 20 | |
| WHITE BLOOD CELL COUNT DECREASED | | | |
| subjects affected / exposed | 24 / 196 (12.24%) | 18 / 198 (9.09%) | |
| occurrences (all) | 43 | 35 | |
| Injury, poisoning and procedural complications | | | |
| INFUSION RELATED REACTION | | | |
| subjects affected / exposed | 8 / 196 (4.08%) | 10 / 198 (5.05%) | |
| occurrences (all) | 9 | 13 | |
| Nervous system disorders | | | |
| DIZZINESS | | | |
| subjects affected / exposed | 11 / 196 (5.61%) | 19 / 198 (9.60%) | |
| occurrences (all) | 14 | 22 | |
| HEADACHE | | | |
| subjects affected / exposed | 23 / 196 (11.73%) | 24 / 198 (12.12%) | |
| occurrences (all) | 25 | 28 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 67 / 196 (34.18%) | 84 / 198 (42.42%) | |
| occurrences (all) | 83 | 95 | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 19 / 196 (9.69%) | 24 / 198 (12.12%) | |
| occurrences (all) | 32 | 42 | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 66 / 196 (33.67%) | 71 / 198 (35.86%) | |
| occurrences (all) | 105 | 122 | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 29 / 196 (14.80%) | 31 / 198 (15.66%) | |
| occurrences (all) | 44 | 45 | |
| Gastrointestinal disorders | | | |
| CONSTIPATION | | | |
| subjects affected / exposed | 58 / 196 (29.59%) | 51 / 198 (25.76%) | |
| occurrences (all) | 69 | 61 | |

| | | | |
|---|---|---|---|
| DIARRHOEA | | | |
| subjects affected / exposed | 30 / 196 (15.31%) | 32 / 198 (16.16%) | |
| occurrences (all) | 46 | 42 | |
| NAUSEA | | | |
| subjects affected / exposed | 64 / 196 (32.65%) | 74 / 198 (37.37%) | |
| occurrences (all) | 89 | 99 | |
| STOMATITIS | | | |
| subjects affected / exposed | 9 / 196 (4.59%) | 11 / 198 (5.56%) | |
| occurrences (all) | 9 | 11 | |
| VOMITING | | | |
| subjects affected / exposed | 31 / 196 (15.82%) | 38 / 198 (19.19%) | |
| occurrences (all) | 45 | 47 | |
| Skin and subcutaneous tissue disorders | | | |
| ALOPECIA | | | |
| subjects affected / exposed | 68 / 196 (34.69%) | 73 / 198 (36.87%) | |
| occurrences (all) | 71 | 75 | |
| PRURITUS | | | |
| subjects affected / exposed | 9 / 196 (4.59%) | 12 / 198 (6.06%) | |
| occurrences (all) | 10 | 12 | |
| RASH | | | |
| subjects affected / exposed | 11 / 196 (5.61%) | 14 / 198 (7.07%) | |
| occurrences (all) | 13 | 21 | |
| RASH MACULO−PAPULAR | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 10 / 198 (5.05%) | |
| occurrences (all) | 3 | 10 | |
| Endocrine disorders | | | |
| HYPERTHYROIDISM | | | |
| subjects affected / exposed | 5 / 196 (2.55%) | 11 / 198 (5.56%) | |
| occurrences (all) | 5 | 11 | |
| HYPOTHYROIDISM | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 20 / 198 (10.10%) | |
| occurrences (all) | 1 | 20 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 13 / 196 (6.63%) | 18 / 198 (9.09%) | |
| occurrences (all) | 16 | 20 | |

| | | | |
|---|---|---|---|
| BACK PAIN | | | |
| subjects affected / exposed | 19 / 196 (9.69%) | 17 / 198 (8.59%) | |
| occurrences (all) | 21 | 17 | |
| MUSCULOSKELETAL PAIN | | | |
| subjects affected / exposed | 11 / 196 (5.61%) | 12 / 198 (6.06%) | |
| occurrences (all) | 13 | 14 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 6 / 196 (3.06%) | 13 / 198 (6.57%) | |
| occurrences (all) | 7 | 13 | |
| Infections and infestations | | | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 16 / 196 (8.16%) | 14 / 198 (7.07%) | |
| occurrences (all) | 19 | 16 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 5 / 196 (2.55%) | 12 / 198 (6.06%) | |
| occurrences (all) | 5 | 16 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 36 / 196 (18.37%) | 54 / 198 (27.27%) | |
| occurrences (all) | 39 | 62 | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 17 / 196 (8.67%) | 8 / 198 (4.04%) | |
| occurrences (all) | 18 | 8 | |
| HYPOMAGNESAEMIA | | | |
| subjects affected / exposed | 9 / 196 (4.59%) | 12 / 198 (6.06%) | |
| occurrences (all) | 9 | 17 | |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 12 / 196 (6.12%) | 10 / 198 (5.05%) | |
| occurrences (all) | 14 | 10 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 25 August 2016 | Protocol was amended to include change of phase from Phase III to Phase I/III. A secondary objective and corresponding outcome measure has been added to evaluate the efficacy of atezolizumab + carboplatin + etoposide compared with placebo + carboplatin + etoposide as measured by investigator-assessed time to response (TTR). TTR will be assessed in the intent-to-treat (ITT) population for patients who had an objective response as determined by the investigator according to RECIST v1.1. Clarifications were made around eligibility criteria and study conduct. |
| 29 August 2017 | Protocol was amended to include modifications to the statistical analysis plan and the timing for the efficacy analyses for progression-free survival (PFS) and overall survival (OS). |
| 06 March 2019 | Protocol was amended to include additional language to the end of study definition to clarify that if the Sponsor decides to terminate the study, subjects who are still receiving study treatment or are in survival follow-up may be enrolled into an extension study or non-interventional study. The timing of the interim and final analysis were modified to be aligned with the statistical analysis plan. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported