



Clinical trial results:

A randomised non-comparative open label phase II trial of atezolizumab plus bevacizumab, with carboplatin-paclitaxel or pemetrexed, in EGFR mutant non-small cell lung carcinoma with acquired resistance

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2019-001687-30 |
| Trial protocol | ES DE |
| Global end of trial date | 22 July 2024 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 06 March 2026 |
| First version publication date | 06 March 2026 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | ETOP 15-19 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-----------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04245085 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Roche Number: MO40586 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | ETOP IBCSG Partners Foundation |
| Sponsor organisation address | Effingerstrasse 33, Bern, Switzerland, 3008 |
| Public contact | ETOP IBCSG Partners Coordinating Center, ETOP IBCSG Partners Foundation, +41 315119400, etop-regulatory@etop.ibcsg.org |
| Scientific contact | ETOP IBCSG Partners Coordinating Center, ETOP IBCSG Partners Foundation, +41 315119400, etop-regulatory@etop.ibcsg.org |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 01 December 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 September 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 July 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to explore the clinical efficacy of atezolizumab and bevacizumab combined with chemotherapy in EGFR mutated patients after failure of standard EGFR targeted therapies.

Protection of trial subjects:

Participating institutions' ethics committees or Institutional Review Boards approved the trial according to local laws and regulations. All patients gave written informed consent, and the trial was performed in compliance with the Helsinki Declaration. The Data Safety and Monitoring Board reviewed the data from this research throughout the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 29 September 2020 |
| 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 | Korea, Democratic People's Republic of: 41 |
| Country: Number of subjects enrolled | Switzerland: 11 |
| Country: Number of subjects enrolled | Singapore: 10 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Spain: 32 |
| Worldwide total number of subjects | 95 |
| EEA total number of subjects | 33 |

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) | 58 |
| From 65 to 84 years | 36 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Overall, 95 patients were registered and randomized in iBiobank from September 29, 2020 until September 12, 2022 (randomization date of the last patient). Randomized patients come from ten centers in Spain, three in Switzerland, two in South Korea, one in Singapore and one in Germany.

Pre-assignment

Screening details:

There were 25 screening failures.

Period 1

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

Arms

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

Arm description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit.

Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Carboplatin: Patients in treatment Arm A will receive carboplatin, AUC5 every 3 weeks for 4-6 cycles.

Paclitaxel: Patients in treatment Arm A will receive paclitaxel, 175-200 mg/m² (at the investigators' discretion), every 3 weeks for 4-6 cycles.

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Atezolizumab |
| Investigational medicinal product code | |
| Other name | Tecentriq |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1200 mg i.v. on day one of every 3-week (+/-3 days) cycle, until PD1, refusal or unacceptable toxicity

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | Avastin |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

15mg/kg i.v. on day one of every 3-week (+/-3 days) cycle, until PD, refusal or unacceptable toxicity

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Patients in treatment Arm A will receive carboplatin, AUC5 plus paclitaxel, 175-200 mg/m², at the investigator's discretion, every 3 weeks for 4-6 cycles.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Patients in treatment Arm A will receive carboplatin, AUC5 plus paclitaxel, 175-200 mg/m², at the investigator's discretion, every 3 weeks for 4-6 cycles.

| | |
|------------------|-------|
| Arm title | Arm B |
|------------------|-------|

Arm description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit.

Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Pemetrexed: Patients in treatment Arm B will receive Pemetrexed, 500 mg/m² every 3 weeks until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Atezolizumab |
| Investigational medicinal product code | |
| Other name | Tecentriq |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1200 mg i.v. on day one of every 3-week (+/-3 days) cycle, until PD1, refusal or unacceptable toxicity

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | Avastin |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

15mg/kg i.v. on day one of every 3-week (+/-3 days) cycle, until PD, refusal or unacceptable toxicity

| | |
|--|--|
| Investigational medicinal product name | Pemetrexed |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

500 mg/m², Q3W, until PD

| Number of subjects in period 1 | Arm A | Arm B |
|---------------------------------------|-------|-------|
| Started | 45 | 50 |
| Completed | 16 | 20 |
| Not completed | 29 | 30 |
| Death | 26 | 27 |
| Withdrawal/Lost to follow-up | 3 | 3 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------|
| Reporting group title | Arm A |
|-----------------------|-------|

Reporting group description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit.

Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Carboplatin: Patients in treatment Arm A will receive carboplatin, AUC5 every 3 weeks for 4-6 cycles.

Paclitaxel: Patients in treatment Arm A will receive paclitaxel, 175-200 mg/m² (at the investigators' discretion), every 3 weeks for 4-6 cycles.

| | |
|-----------------------|-------|
| Reporting group title | Arm B |
|-----------------------|-------|

Reporting group description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit.

Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Pemetrexed: Patients in treatment Arm B will receive Pemetrexed, 500 mg/m² every 3 weeks until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment

| Reporting group values | Arm A | Arm B | Total |
|--|----------|----------|-------|
| Number of subjects | 45 | 50 | 95 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 61 | 63 | |
| full range (min-max) | 32 to 93 | 45 to 75 | - |

| | | | |
|--|----|----|----|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 27 | 17 | 44 |
| Male | 18 | 33 | 51 |
| Race/Ethnicity | | | |
| Units: Subjects | | | |
| Asian | 25 | 27 | 52 |
| White | 20 | 21 | 41 |
| Black | 0 | 1 | 1 |
| Other | 0 | 1 | 1 |
| ECOG Performance Status | | | |
| 0: Fully active, able to carry on all pre-disease performance without restriction; 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; | | | |
| Units: Subjects | | | |
| Status 0 | 16 | 8 | 24 |
| Status 1 | 29 | 42 | 71 |
| Smoking Status | | | |
| Current smoker: Still smokes cigarettes, Former smoker: Smoked at least 100 cigarettes in the past during the whole life, Never smoker: Smoked 0-99 cigarettes during the whole life. | | | |
| Units: Subjects | | | |
| Current smoker | 3 | 4 | 7 |
| Former smoker | 17 | 14 | 31 |
| Never smoked | 25 | 32 | 57 |
| Stage | | | |
| Stage is based on the 8th TNM classification for NSCLC (American Joint Committee on Cancer). Stage IIIB/C: the tumor is 5 cm or smaller (IIIB) or any size (IIIC) and cancer has spread to lymph nodes above the collarbone on the same side of the chest as the primary tumor or to any lymph nodes on the opposite side of the chest as the primary tumor. Stage IVA: cancer has spread within the chest and/or has spread to 1 area outside of the chest. Stage IVB: cancer has spread outside of the chest to more than 1 place in 1 organ or to more than 1 organ. | | | |
| Units: Subjects | | | |
| IIIB | 1 | 0 | 1 |
| IVA | 10 | 21 | 31 |
| IVB | 34 | 29 | 63 |
| EGFR mutation type | | | |
| Histologically or cytologically confirmed exon 19 deletion or exon 21 L858R mutation by a certified local laboratory | | | |
| Units: Subjects | | | |
| Exon 19 deletion | 28 | 29 | 57 |
| Exon 21 L858R | 16 | 19 | 35 |
| Other | 1 | 2 | 3 |
| Prior TKI treatment | | | |
| TKI: tyrosine kinase inhibitors | | | |
| Units: Subjects | | | |
| Afatinib | 9 | 8 | 17 |
| Erlotinib | 2 | 3 | 5 |
| Gefitinib | 4 | 5 | 9 |
| Lazertinib | 1 | 5 | 6 |
| Nazartinib | 1 | 0 | 1 |
| Osimertinib | 28 | 27 | 55 |
| Osimertinib or Lazertinib | 0 | 1 | 1 |
| Osimertinib or Savolitinib | 0 | 1 | 1 |

| | | | |
|------------------|----|----|----|
| Brain metastasis | | | |
| Units: Subjects | | | |
| Yes | 15 | 16 | 31 |
| No | 30 | 34 | 64 |

End points

End points reporting groups

| | |
|-----------------------|-------|
| Reporting group title | Arm A |
|-----------------------|-------|

Reporting group description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit.

Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Carboplatin: Patients in treatment Arm A will receive carboplatin, AUC5 every 3 weeks for 4-6 cycles.

Paclitaxel: Patients in treatment Arm A will receive paclitaxel, 175-200 mg/m² (at the investigators' discretion), every 3 weeks for 4-6 cycles.

| | |
|-----------------------|-------|
| Reporting group title | Arm B |
|-----------------------|-------|

Reporting group description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit.

Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Pemetrexed: Patients in treatment Arm B will receive Pemetrexed, 500 mg/m² every 3 weeks until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment

Primary: Progression-free rate at 12 months

| | |
|-----------------|------------------------------------|
| End point title | Progression-free rate at 12 months |
|-----------------|------------------------------------|

End point description:

Progression-Free Survival (PFS) rate at 12-months is defined as the rate of patients without a PFS event at 12 months from randomisation. PFS is defined as the time from the date of randomisation until documented progression (according to RECIST v1.1) or death, if progression is not documented. Censoring (for patients without a PFS/death event) will occur at the last tumour assessment if the patient is lost to follow-up or refuses further documentation of follow-up.

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

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

| End point values | Arm A | Arm B | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 ^[1] | 45 ^[2] | | |
| Units: Patients | 9 | 21 | | |

Notes:

[1] - Primary efficacy cohort, randomised patients who are not lost from follow-up before a progression-free survival event or earlier than 1 year follow-up

[2] - Primary efficacy cohort, randomised patients who are not lost from follow-up before a progression-free survival event or earlier than 1 year follow-up

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---------------------------|
| Comparison groups | Arm B v Arm A |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.367 ^[3] |
| Method | Exact binomial one-sample |
| Parameter estimate | proportion |
| Point estimate | 20.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10 |
| upper limit | 36 |

Notes:

[3] - 1-sided significance level of 2.5%

| Statistical analysis title | Statistical Analysis 2 |
|--|---------------------------|
| Statistical analysis description: | |
| The study was designed to test the primary efficacy hypothesis that 14 or more patients among the 45 evaluable in each treatment arm should be progression-free in the 12-month timepoint in order to reject the null hypothesis H0: 12-month PFS rate (π_0) ≤ 0.18 , versus the alternative hypothesis H1: 12-month PFS rate (π_1) > 0.18 , evaluated at $\alpha = 0.025$. The rate of progression-free patients at 12 months will be accompanied by 2-sided 95% exact binomial CI. | |
| Comparison groups | Arm A v Arm B |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.174 ^[4] |
| Method | Exact binomial one-sample |
| Parameter estimate | proportion |
| Point estimate | 24.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.9 |
| upper limit | 39.5 |

Notes:

[4] - 1-sided significance level of 2.5%

Secondary: Objective response (OR)

| | |
|-----------------|-------------------------|
| End point title | Objective response (OR) |
|-----------------|-------------------------|

End point description:

Objective response is defined as best overall response (CR or PR) across all assessment time-points according to RECIST v1.1, from randomisation until either the end of protocol treatment or the end of follow-up.

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

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

| End point values | Arm A | Arm B | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 ^[5] | 50 ^[6] | | |
| Units: Participant | 21 | 16 | | |

Notes:

[5] - Intention-To-Treat cohort of all randomised patients

[6] - Intention-To-Treat cohort of all randomised patients

Statistical analyses

No statistical analyses for this end point

Secondary: Extra-cranial Progression-free survival (ecPFS)

| | |
|-----------------|---|
| End point title | Extra-cranial Progression-free survival (ecPFS) |
|-----------------|---|

End point description:

Extra-cranial progression-free-survival is the time from randomisation to documentation of disease progression outside the central nervous system (CNS) as per RECIST v1.1 or death, whichever occurred first.

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

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

| End point values | Arm A | Arm B | | |
|----------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 50 | | |
| Units: Molar nth | | | | |
| median (confidence interval 95%) | 7.8 (5.5 to 9.7) | 9.2 (4.9 to 9.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Intra-cranial Progression-free survival (icPFS)

| | |
|-----------------|---|
| End point title | Intra-cranial Progression-free survival (icPFS) |
|-----------------|---|

End point description:

Intracranial progression-free-survival is defined as the time from randomisation to first documented

radiographic evidence of CNS progression. CNS progression is defined as progression due to newly developed CNS lesions and/or progression of pre-existing baseline CNS lesions.

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

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

| End point values | Arm A | Arm B | | |
|----------------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 ^[7] | 50 ^[8] | | |
| Units: Month | | | | |
| median (confidence interval 95%) | 8.3 (5.7 to 15.4) | 12.3 (9.8 to 15.8) | | |

Notes:

[7] - Intention-To-Treat cohort of all randomised patients

[8] - Intention-To-Treat cohort of all randomised patients

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall survival (OS) |
|-----------------|-----------------------|

End point description:

OS is defined as the time from the date of randomisation until death from any cause. Censoring will occur at the last follow-up date.

BECAUSE THE SYSTEM DOES NOT ALLOW EMPTY VALUES IN THE RESULTS SECTION, THEY ARE ADDED BELOW INSTEAD:

Arm B

Median: 15.6, 95%CI: 11.8 to NA, the upper 95% confidence limit is not estimable.

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

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

| End point values | Arm A | Arm B | | |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 ^[9] | 50 ^[10] | | |
| Units: Month | | | | |
| median (confidence interval 95%) | 15.4 (9.4 to 23.9) | 0 (0 to 0) | | |

Notes:

[9] - Intention-To-Treat cohort of all randomised patients

[10] - Intention-To-Treat cohort of all randomised patients

Statistical analyses

Secondary: Time to deterioration (TTD) assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30)

| | |
|-----------------|---|
| End point title | Time to deterioration (TTD) assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) |
|-----------------|---|

End point description:

Deterioration is defined as the first time that patient's score for Global health status/QoL shows a ≥ 10 -point decrease from baseline. Deterioration must be held for at least two consecutive assessments or be followed by PD and/or death within the next 3 weeks.

BECAUSE THE SYSTEM DOES NOT ALLOW EMPTY VALUES IN THE RESULTS SECTION, THEY ARE ADDED BELOW INSTEAD:

Results Arm A

Median: 7.2, 95%CI 2.7 to NA, the upper 95% confidence limit is not estimable.

Results Arm B

Median: NA, 95%CI 3.5 to NA, median deterioration time and upper 95% confidence limit are not estimable.

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

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

| End point values | Arm A | Arm B | | |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 ^[11] | 48 ^[12] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 0 (0 to 0) | 0 (0 to 0) | | |

Notes:

[11] - QoL cohort (at least 1 dose of treatment, with baseline QoL assessment and post-baseline QoL forms)

[12] - QoL cohort (at least 1 dose of treatment, with baseline QoL assessment and post-baseline QoL forms)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to deterioration (TTD) assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire lung cancer-specific module (QLQ-LC13)

| | |
|-----------------|--|
| End point title | Time to deterioration (TTD) assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire lung cancer-specific module (QLQ-LC13) |
|-----------------|--|

End point description:

Deterioration is defined as the first time that patient's score for Cough QLQ-LC13 symptom shows a ≥ 10 -point decrease from baseline. Deterioration must be held for at least two consecutive assessments or be followed by PD and/or death within the next 3 weeks.

BECAUSE THE SYSTEM DOES NOT ALLOW EMPTY VALUES IN THE RESULTS SECTION, THEY ARE ADDED BELOW INSTEAD:

Arm A

Median: NA, 95%CI: 8.6 to NA, median deterioration time and upper 95% confidence limit are not estimable.

Arm B

Median: NA, 95%CI: NA to NA, median deterioration time and lower and upper 95% confidence limit are not estimable.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Evaluated up to approximately 36 months from the randomisation of the first patient. | |

| End point values | Arm A | Arm B | | |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 ^[13] | 48 ^[14] | | |
| Units: Month | | | | |
| median (confidence interval 95%) | 0 (0 to 0) | 0 (0 to 0) | | |

Notes:

[13] - QoL cohort (at least 1 dose of treatment, with baseline QoL assessment and post-baseline QoL forms)

[14] - QoL cohort (at least 1 dose of treatment, with baseline QoL assessment and post-baseline QoL forms)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

| | |
|--|---------------------------|
| End point title | Progression-Free Survival |
| End point description: | |
| PFS is defined as the time from the date of randomisation until documented progression (according to RECIST v1.1) or death, if progression is not documented. Censoring (for patients without a PFS/death event) will occur at the last tumour assessment if the patient is lost to follow-up or refuses further documentation of follow-up. | |
| End point type | Secondary |
| End point timeframe: | |
| Evaluated up to approximately 36 months from the randomisation of the first patient. | |

| End point values | Arm A | Arm B | | |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 ^[15] | 50 ^[16] | | |
| Units: Month | | | | |
| median (confidence interval 95%) | 6.4 (5.3 to 8.3) | 7.6 (4.1 to 9.7) | | |

Notes:

[15] - Intention-To-Treat cohort of all randomised patients

[16] - Intention-To-Treat cohort of all randomised patients

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events

| | |
|-----------------|----------------|
| End point title | Adverse Events |
|-----------------|----------------|

End point description:

Adverse events, graded by CTCAE version 5.0, will be recorded from date of signature of informed consent until 90 days after all trial treatment discontinuation.

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

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

| End point values | Arm A | Arm B | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 ^[17] | 50 ^[18] | | |
| Units: Participant | | | | |
| Experienced AE/SAE | 43 | 49 | | |
| No AE/SAE | 1 | 1 | | |
| Experienced SAE | 19 | 23 | | |

Notes:

[17] - Safety population (all patients who received at least 1 dose of trial treatment).

[18] - Safety population (all patients who received at least 1 dose of trial treatment).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs were reported from the date randomisation until 90 days after the last dose of protocol treatment.

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

Dictionary used

| | |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

| | |
|--------------------|-----|
| Dictionary version | 5.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|-------|
| Reporting group title | Arm A |
|-----------------------|-------|

Reporting group description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit. Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Carboplatin: Patients in treatment Arm A will receive carboplatin, AUC5 every 3 weeks for 4-6 cycles. Paclitaxel: Patients in treatment Arm A will receive paclitaxel, 175-200 mg/m² (at the investigators' discretion), every 3 weeks for 4-6 cycles.

| | |
|-----------------------|-------|
| Reporting group title | Arm B |
|-----------------------|-------|

Reporting group description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit. Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Pemetrexed: Patients in treatment Arm B will receive Pemetrexed, 500 mg/m² every 3 weeks until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

| Serious adverse events | Arm A | Arm B | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 19 / 44 (43.18%) | 23 / 50 (46.00%) | |
| number of deaths (all causes) | 3 | 3 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Synchronous urothelial carcinoma | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thromboembolic event | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 50 (4.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 4 / 50 (8.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medically assisted suicide | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease (COPD) | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnea | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxemic respiratory failure | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fracture | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 2 / 50 (4.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Encephalitis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paresthesia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stroke | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Transient ischemic attacks | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucositis oral | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Cholangitis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Pressure ulcers | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Anorectal infection | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial infection | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 infection | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 4 / 50 (8.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (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 / 44 (6.82%) | 3 / 50 (6.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Meningitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shingles | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (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 / 44 (4.55%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperuricemia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatremia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 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 | Arm A | Arm B | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 43 / 44 (97.73%) | 49 / 50 (98.00%) | |
| Vascular disorders | | | |
| Arterial thromboembolism | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hot flashes | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Hypertension | | | |
| subjects affected / exposed | 10 / 44 (22.73%) | 17 / 50 (34.00%) | |
| occurrences (all) | 10 | 17 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Thromboembolic event | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) | |
| occurrences (all) | 1 | 1 | |
| Surgical and medical procedures | | | |
| Prophylactic femoral intramedullary nailing | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) | |
| occurrences (all) | 1 | 1 | |
| Chills | | | |

| | | |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 0 | 2 |
| Edema face | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 3 / 50 (6.00%) |
| occurrences (all) | 0 | 3 |
| Edema limbs | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 6 / 50 (12.00%) |
| occurrences (all) | 2 | 6 |
| Fatigue | | |
| subjects affected / exposed | 13 / 44 (29.55%) | 16 / 50 (32.00%) |
| occurrences (all) | 13 | 16 |
| Fever | | |
| subjects affected / exposed | 6 / 44 (13.64%) | 3 / 50 (6.00%) |
| occurrences (all) | 6 | 3 |
| Flu like symptoms | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) |
| occurrences (all) | 1 | 1 |
| General deterioration | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| General discomfort | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| General weakness | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 1 / 50 (2.00%) |
| occurrences (all) | 2 | 1 |
| Generalized edema | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 3 / 50 (6.00%) |
| occurrences (all) | 0 | 3 |
| Infusion site extravasation | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Localized edema | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Malaise | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 50 (4.00%) | |
| occurrences (all) | 0 | 2 | |
| Night sweat | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Non cardiac chest pain | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 5 / 50 (10.00%) | |
| occurrences (all) | 3 | 5 | |
| Pain | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 9 / 50 (18.00%) | |
| occurrences (all) | 4 | 9 | |
| Poor general condition | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Poor oral intake | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) | |
| occurrences (all) | 1 | 1 | |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) | |
| occurrences (all) | 1 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute bronchitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Aspiration | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 50 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood tinged sputum | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Chronic obstructive pulmonary disease (COPD) | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Cough | | | |

| | | |
|-----------------------------|-----------------|------------------|
| subjects affected / exposed | 6 / 44 (13.64%) | 6 / 50 (12.00%) |
| occurrences (all) | 6 | 6 |
| Dysphonia | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 0 |
| Dyspnea | | |
| subjects affected / exposed | 5 / 44 (11.36%) | 11 / 50 (22.00%) |
| occurrences (all) | 5 | 11 |
| Epistaxis | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 4 / 50 (8.00%) |
| occurrences (all) | 3 | 4 |
| Hiccups | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Hoarseness | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 2 / 50 (4.00%) |
| occurrences (all) | 2 | 2 |
| Laryngeal hemorrhage | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Pleural effusion | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 4 / 50 (8.00%) |
| occurrences (all) | 2 | 4 |
| Pneumonitis | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Productive cough | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pulmonary edema | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 0 | 2 |
| Retrosternal pain | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Rhinorrhea | | |

| | | | |
|--|----------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 2 / 50 (4.00%) 2 | |
| Sputum subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 2 / 50 (4.00%) 2 | |
| Psychiatric disorders | | | |
| Agitation subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 50 (0.00%) 0 | |
| Anxiety subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 3 / 50 (6.00%) 3 | |
| Confusion subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 50 (0.00%) 0 | |
| Depression subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 1 / 50 (2.00%) 1 | |
| Insomnia subjects affected / exposed occurrences (all) | 3 / 44 (6.82%) 3 | 5 / 50 (10.00%) 5 | |
| Low mood subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 6 / 44 (13.64%) 6 | 13 / 50 (26.00%) 13 | |
| Alkaline phosphatase increased subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 5 / 50 (10.00%) 5 | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 7 / 44 (15.91%) 7 | 19 / 50 (38.00%) 19 | |
| BUN increased | | | |

| | | |
|---------------------------------------|------------------|-----------------|
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood bilirubin increased | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood lactate dehydrogenase increased | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 4 / 50 (8.00%) |
| occurrences (all) | 0 | 4 |
| Cholesterol high | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) |
| occurrences (all) | 1 | 1 |
| Creatinine increased | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 5 / 50 (10.00%) |
| occurrences (all) | 1 | 5 |
| GGT increased | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 9 / 50 (18.00%) |
| occurrences (all) | 1 | 9 |
| Leukocytes count decreased | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 0 |
| Lipase increased | | |
| subjects affected / exposed | 5 / 44 (11.36%) | 3 / 50 (6.00%) |
| occurrences (all) | 5 | 3 |
| Neutrophil count decreased | | |
| subjects affected / exposed | 12 / 44 (27.27%) | 4 / 50 (8.00%) |
| occurrences (all) | 12 | 4 |
| Platelet count decreased | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 1 / 50 (2.00%) |
| occurrences (all) | 3 | 1 |
| Serum amylase increased | | |
| subjects affected / exposed | 8 / 44 (18.18%) | 8 / 50 (16.00%) |
| occurrences (all) | 8 | 8 |
| Transaminitis | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |

| | | | |
|--|---------------------|---------------------|--|
| Weight loss subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 2 / 50 (4.00%) 2 | |
| White blood cell decreased subjects affected / exposed occurrences (all) | 4 / 44 (9.09%) 4 | 0 / 50 (0.00%) 0 | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 50 (0.00%) 0 | |
| Fall subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 2 / 50 (4.00%) 2 | |
| Infusion related reaction subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 1 / 50 (2.00%) 1 | |
| Seroma subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Vaccination complication subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Wound dehiscence subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 50 (0.00%) 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Chest pain cardiac subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Palpitations subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 50 (0.00%) 0 | |
| Pericardial effusion | | | |

| | | | |
|-------------------------------|------------------|------------------|--|
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 4 / 50 (8.00%) | |
| occurrences (all) | 0 | 4 | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 2 / 50 (4.00%) | |
| occurrences (all) | 1 | 2 | |
| Dysphasia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Headache | | | |
| subjects affected / exposed | 6 / 44 (13.64%) | 10 / 50 (20.00%) | |
| occurrences (all) | 6 | 10 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) | |
| occurrences (all) | 1 | 1 | |
| Neurotoxicity | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neurotoxicity in hands | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Paresthesia | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 1 / 50 (2.00%) | |
| occurrences (all) | 4 | 1 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 15 / 44 (34.09%) | 3 / 50 (6.00%) | |
| occurrences (all) | 15 | 3 | |

| | | | |
|--|------------------------|----------------------|--|
| Recurrent laryngeal nerve palsy subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Seizure subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 50 (0.00%) 0 | |
| Syncope subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 50 (0.00%) 0 | |
| Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all) | 11 / 44 (25.00%) 11 | 7 / 50 (14.00%) 7 | |
| Febrile neutropenia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Nose bleeding subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Thrombotic microangiopathy subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 50 (0.00%) 0 | |
| Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Eye disorders Blepharitis subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Blurred vision subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 2 / 50 (4.00%) 2 | |
| Cataract | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Dry eye | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 1 / 50 (2.00%) | |
| occurrences (all) | 2 | 1 | |
| Periorbital oedema | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Vision decreased | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Watering eyes | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 5 / 50 (10.00%) | |
| occurrences (all) | 4 | 5 | |
| Anal fissure | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Anal hemorrhage | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Bloating | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bowel rhythm change | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |

| | | |
|---------------------------------|------------------|------------------|
| Colonic hemorrhage | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Constipation | | |
| subjects affected / exposed | 12 / 44 (27.27%) | 15 / 50 (30.00%) |
| occurrences (all) | 12 | 15 |
| Dental caries | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) |
| occurrences (all) | 1 | 1 |
| Diarrhea | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 8 / 50 (16.00%) |
| occurrences (all) | 3 | 8 |
| Diverticulitis | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Dry mouth | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 0 | 2 |
| Dyspepsia | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 4 / 50 (8.00%) |
| occurrences (all) | 3 | 4 |
| Epigastric pain | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Esophageal spasm | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 0 |
| Esophagitis | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Gastroesophageal reflux disease | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 0 | 2 |
| Gastrointestinal pain | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |

| | | | |
|---|------------------------|------------------------|--|
| Gum inflammation subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Hemorrhoids subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 3 | 1 / 50 (2.00%) 1 | |
| Ileus subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 50 (0.00%) 0 | |
| Mucositis oral subjects affected / exposed occurrences (all) | 4 / 44 (9.09%) 4 | 3 / 50 (6.00%) 3 | |
| Nausea subjects affected / exposed occurrences (all) | 13 / 44 (29.55%) 13 | 18 / 50 (36.00%) 18 | |
| Periodontal disease subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 1 / 50 (2.00%) 1 | |
| Pyrosis subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Toothache subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 44 (6.82%) 3 | 6 / 50 (12.00%) 6 | |
| Hepatobiliary disorders Cholangiohepatitis subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Hepatic cytolysis subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Skin and subcutaneous tissue disorders | | | |

| | | |
|--|-----------------|-----------------|
| Alopecia | | |
| subjects affected / exposed | 9 / 44 (20.45%) | 1 / 50 (2.00%) |
| occurrences (all) | 9 | 1 |
| Dry skin | | |
| subjects affected / exposed | 5 / 44 (11.36%) | 2 / 50 (4.00%) |
| occurrences (all) | 5 | 2 |
| Eczema | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Mucositis in hands | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 0 |
| Palmar plantar erythrodysesthesia syndrome | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Pruritus | | |
| subjects affected / exposed | 7 / 44 (15.91%) | 5 / 50 (10.00%) |
| occurrences (all) | 7 | 5 |
| Pustules | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Rash acneiform | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 3 / 50 (6.00%) |
| occurrences (all) | 1 | 3 |
| Rash eczematiform | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Rash maculo papular | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 5 / 50 (10.00%) |
| occurrences (all) | 4 | 5 |
| Skin induration | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Skin rash | | |

| | | | |
|---|------------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 3 / 50 (6.00%) 3 | |
| Toxicoderma subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Umbilical hernia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Urticaria subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 50 (0.00%) 0 | |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 4 / 50 (8.00%) 4 | |
| Proteinuria subjects affected / exposed occurrences (all) | 12 / 44 (27.27%) 12 | 9 / 50 (18.00%) 9 | |
| Urinary frequency subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 50 (2.00%) 1 | |
| Urinary retention subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 0 / 50 (0.00%) 0 | |
| Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 3 / 50 (6.00%) 3 | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 4 / 44 (9.09%) 4 | 4 / 50 (8.00%) 4 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 7 / 44 (15.91%) 7 | 4 / 50 (8.00%) 4 | |
| Back pain | | | |

| | | |
|---------------------------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 3 / 50 (6.00%) |
| occurrences (all) | 0 | 3 |
| Bone pain | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 4 / 50 (8.00%) |
| occurrences (all) | 2 | 4 |
| Flank pain | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 3 / 50 (6.00%) |
| occurrences (all) | 1 | 3 |
| Generalized muscle weakness | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hip pain | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Joint range of motion decreased | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Lumbar pain | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Myalgia | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 2 / 50 (4.00%) |
| occurrences (all) | 3 | 2 |
| Neck pain | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) |
| occurrences (all) | 1 | 1 |
| Other | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pain in extremity | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 1 / 50 (2.00%) |
| occurrences (all) | 2 | 1 |
| Shoulder and pelvic girdle pain | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 1 |
| Tingling (fingers, toes) | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 50 (0.00%) 0 | |
| Infections and infestations | | | |
| Belly button infection | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| C reactive protein increased | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| COVID 19 infection | | | |
| subjects affected / exposed | 9 / 44 (20.45%) | 7 / 50 (14.00%) | |
| occurrences (all) | 9 | 7 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gum infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hepatitis viral | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Herpes simplex reactivation | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 2 / 50 (4.00%) | |
| occurrences (all) | 1 | 2 | |
| Mucosal infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) | |
| occurrences (all) | 1 | 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|------------------------------------|-----------------|------------------|--|
| Shingles | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Skin infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 2 / 50 (4.00%) | |
| occurrences (all) | 1 | 2 | |
| Upper respiratory infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 50 (2.00%) | |
| occurrences (all) | 1 | 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 4 / 50 (8.00%) | |
| occurrences (all) | 1 | 4 | |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 5 / 44 (11.36%) | 11 / 50 (22.00%) | |
| occurrences (all) | 5 | 11 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Hypercalcemia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperkalemia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 4 / 50 (8.00%) | |
| occurrences (all) | 0 | 4 | |
| Hypoglycemia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 50 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypokalemia | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 3 / 50 (6.00%) | |
| occurrences (all) | 2 | 3 | |
| Hypomagnesemia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 3 / 44 (6.82%) | 1 / 50 (2.00%) | |
| occurrences (all) | 3 | 1 | |
| Hyponatremia | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 2 / 50 (4.00%) | |
| occurrences (all) | 3 | 2 | |
| Hyporeflexia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Hypovitaminose D | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |
| Iron deficiency | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|---|
| 04 June 2021 | <p>During the submission process of the first protocol version ETOP received several requests for protocol changes from authorities in various countries. Main change requests concerned recommendations for the paclitaxel dosing, in particular for the Asian population, and some clarification regarding the eligibility criteria for the liver and renal function, as well as for EGFR status.</p> <p>Furthermore, the amendment accounts for the new safety information for atezolizumab, including the addition of the newly identified risks of Severe Cutaneous Adverse Reactions (SCARs). The management of atezolizumab-related toxicities has been updated based on the latest version of the atezolizumab IB Version 15, July 2019, the Addendum 2, December 2019 to the IB V15. The diagnostic criteria and management guidelines for haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), replacing systemic immune activation (SIS), were updated according to a separate Safety Memorandum from Roche.</p> <p>In addition, the list of AESIs has been updated to reflect the new safety information and history of active diverticulitis has been added to the exclusion criteria.</p> <p>Furthermore, some minor protocol clarifications have been added and ambiguities and typos eliminated.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported