



Clinical trial results:

A Randomized, Placebo-Controlled, Double-Blind Phase 3 Study to Evaluate the Efficacy and Safety of Tislelizumab (BGB-A317) in Combination with Chemotherapy as First-Line Treatment in Patients with Unresectable, Locally Advanced Recurrent or Metastatic Esophageal Squamous Cell Carcinoma.

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2018-000587-28 |
| Trial protocol | DE GB FR BE ES PL CZ IT RO |
| Global end of trial date | 22 August 2024 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 19 June 2025 |
| First version publication date | 19 June 2025 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | BGB-A317-306 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03783442 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | BeiGene |
| Sponsor organisation address | 311 Pennington-Rocky Hill Rd, Pennington, NJ, United States, 08534 |
| Public contact | BeiGene Clinical Support, BeiGene, Ltd., 1 877-828-5568, clinicaltrials@beigene.com |
| Scientific contact | BeiGene Clinical Support, BeiGene, Ltd., 1 877-828-5568, clinicaltrials@beigene.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 22 August 2024 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 August 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate and compare the overall survival (OS) following treatment with tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy when given as first-line treatment in patients with unresectable, locally advanced recurrent or metastatic esophageal squamous cell carcinoma (ESCC).

Protection of trial subjects:

This study was conducted in accordance with BeiGene procedures, which comply with the principles of Good Clinical Practice, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, the Declaration of Helsinki, and local regulatory requirements.

The protocol, any amendments, and informed consent forms (ICFs) were reviewed and approved by the Independent Ethics Committees (IEC)/Institutional Review Board (IRB) in conformance with Good Clinical Practice and applicable regulatory requirements.

The IEC/IRB-approved ICF was signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. A copy of each signed ICF was provided to the patient or the patient's legally authorized representative.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 11 December 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | China: 355 |
| Country: Number of subjects enrolled | Japan: 66 |
| Country: Number of subjects enrolled | Korea, Republic of: 50 |
| Country: Number of subjects enrolled | Taiwan: 15 |
| Country: Number of subjects enrolled | Australia: 5 |
| Country: Number of subjects enrolled | Russian Federation: 27 |
| Country: Number of subjects enrolled | United States: 2 |
| Country: Number of subjects enrolled | Poland: 15 |
| Country: Number of subjects enrolled | Romania: 7 |
| Country: Number of subjects enrolled | Spain: 23 |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | Belgium: 24 |
| Country: Number of subjects enrolled | Czechia: 2 |
| Country: Number of subjects enrolled | France: 36 |

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Germany: 6 |
| Country: Number of subjects enrolled | Italy: 11 |
| Worldwide total number of subjects | 649 |
| EEA total number of subjects | 124 |

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) | 337 |
| From 65 to 84 years | 312 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 162 centers in 16 countries/regions across Asia, Europe, North America, and Oceania.

Pre-assignment

Screening details:

Participants were randomly assigned (1:1) to either tislelizumab plus investigator-chosen chemotherapy (ICC) or placebo plus ICC.

Randomization was stratified by ICC (platinum plus fluoropyrimidine vs platinum plus paclitaxel), region (Asia [excluding Japan] vs Japan vs other regions), and previous definitive therapy (yes vs no).

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 | Tislelizumab + Chemotherapy |

Arm description:

Participants received tislelizumab 200 mg administered intravenously (IV) on Day 1 of each 3-week treatment cycle together with an investigator-chosen chemotherapy doublet until unacceptable toxicity, disease progression or withdrawal for other reasons.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tislelizumab |
| Investigational medicinal product code | BGB-A317 |
| Other name | TEVIMBRA® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Tislelizumab 200 mg administered by intravenous infusion every 3 weeks.

| | |
|--|---|
| Investigational medicinal product name | Chemotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Chemotherapy options were a platinum agent (cisplatin 60-80 mg/m² intravenously on Day 1 or oxaliplatin 130 mg/m² intravenously on Day 1) combined with a fluoropyrimidine (fluorouracil [750-800 mg/m² intravenously on Days 1-5] or capecitabine [1000 mg/m² orally twice daily on Days 1-14]) or paclitaxel (175 mg/m² intravenously on Day 1).

| | |
|------------------|------------------------|
| Arm title | Placebo + Chemotherapy |
|------------------|------------------------|

Arm description:

Participants received placebo administered IV on Day 1 of each 3-week treatment cycle together with an investigator-chosen chemotherapy doublet until unacceptable toxicity, disease progression or withdrawal for other reasons.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Placebo to tislelizumab administered by intravenous infusion every 3 weeks | |
| Investigational medicinal product name | Chemotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Chemotherapy options were a platinum agent (cisplatin 60-80 mg/m² intravenously on Day 1 or oxaliplatin 130 mg/m² intravenously on Day 1) combined with a fluoropyrimidine (fluorouracil [750-800 mg/m² intravenously on Days 1-5] or capecitabine [1000 mg/m² orally twice daily on Days 1-14]) or paclitaxel (175 mg/m² intravenously on Day 1).

| Number of subjects in period 1 | Tislelizumab + Chemotherapy | Placebo + Chemotherapy |
|---------------------------------------|--------------------------------|---------------------------|
| Started | 326 | 323 |
| Treated | 324 | 321 |
| Completed | 0 | 0 |
| Not completed | 326 | 323 |
| Consent withdrawn by subject | 19 | 21 |
| Sponsor Ended Study | 48 | 28 |
| Death | 252 | 268 |
| Lost to follow-up | 7 | 6 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | Tislelizumab + Chemotherapy |
|-----------------------|-----------------------------|

Reporting group description:

Participants received tislelizumab 200 mg administered intravenously (IV) on Day 1 of each 3-week treatment cycle together with an investigator-chosen chemotherapy doublet until unacceptable toxicity, disease progression or withdrawal for other reasons.

| | |
|-----------------------|------------------------|
| Reporting group title | Placebo + Chemotherapy |
|-----------------------|------------------------|

Reporting group description:

Participants received placebo administered IV on Day 1 of each 3-week treatment cycle together with an investigator-chosen chemotherapy doublet until unacceptable toxicity, disease progression or withdrawal for other reasons.

| Reporting group values | Tislelizumab + Chemotherapy | Placebo + Chemotherapy | Total |
|---|-----------------------------|------------------------|-------|
| Number of subjects | 326 | 323 | 649 |
| Age categorical Units: Subjects | | | |
| < 65 years | 176 | 161 | 337 |
| ≥ 65 years | 150 | 162 | 312 |
| Age continuous Units: years | | | |
| median | 64.0 | 65.0 | |
| full range (min-max) | 26 to 84 | 40 to 84 | - |
| Gender categorical Units: Subjects | | | |
| Female | 44 | 42 | 86 |
| Male | 282 | 281 | 563 |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 1 | 1 |
| Asian | 243 | 243 | 486 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 79 | 76 | 155 |
| Unknown or Not Reported | 4 | 3 | 7 |
| Geographic Region | | | |
| Rest of World includes Europe, North America and Oceania. | | | |
| Units: Subjects | | | |
| Asia (excluding Japan) | 210 | 210 | 420 |
| Japan | 33 | 33 | 66 |
| Rest of World | 83 | 80 | 163 |
| Prior Definitive Therapy Units: Subjects | | | |
| Yes | 152 | 150 | 302 |
| No | 174 | 173 | 347 |
| Investigator Chosen Chemotherapy Units: Subjects | | | |

| | | | |
|--|-----|-----|-----|
| Platinum with Fluoropyrimidine | 147 | 146 | 293 |
| Platinum with Paclitaxel | 179 | 177 | 356 |
| Programmed Cell Death Protein Ligand-1 (PD-L1) Expression | | | |
| <p>PD-L1 is a protein found on some normal cells and in higher-than-normal amounts on certain cancer cells that can block the immune system from attacking cancer cells.</p> <p>PD-L1 expression was assessed by a central laboratory using the tumor area positivity (TAP) score, defined as total percentage of tumor area (tumor and any desmoplastic stroma) covered by tumor cells with PD-L1 membrane staining (any intensity), and tumor associated immune cells with PD-L1 staining (any intensity), visually estimated by pathologists using the Ventana PD-L1 (SP263) assay.</p> | | | |
| Units: Subjects | | | |
| PD-L1 Score \geq 10% | 116 | 107 | 223 |
| PD-L1 Score < 10% | 151 | 168 | 319 |
| Unknown | 59 | 48 | 107 |

End points

End points reporting groups

| | |
|---|-----------------------------|
| Reporting group title | Tislelizumab + Chemotherapy |
| Reporting group description: Participants received tislelizumab 200 mg administered intravenously (IV) on Day 1 of each 3-week treatment cycle together with an investigator-chosen chemotherapy doublet until unacceptable toxicity, disease progression or withdrawal for other reasons. | |
| Reporting group title | Placebo + Chemotherapy |
| Reporting group description: Participants received placebo administered IV on Day 1 of each 3-week treatment cycle together with an investigator-chosen chemotherapy doublet until unacceptable toxicity, disease progression or withdrawal for other reasons. | |

Primary: Overall Survival (OS)

| | |
|---|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: Overall survival is defined as the time from the date of randomization until the date of death due to any cause. Median OS was estimated using the Kaplan-Meier method. The Intent-to-Treat (ITT) Analysis Set included all randomized participants. | |
| End point type | Primary |
| End point timeframe: From randomization to the primary analysis cutoff date of 28 February 2022; maximum time on follow-up was 3 years and 2 months. | |

| End point values | Tislelizumab + Chemotherapy | Placebo + Chemotherapy | | |
|----------------------------------|-----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 323 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 17.2 (15.8 to 20.1) | 10.6 (9.3 to 12.1) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of OS in the ITT Analysis Set |
| Statistical analysis description: The analysis of overall survival was performed using a stratified log-rank test stratified by pooled geographic region, prior definitive therapy and Investigator chemotherapy choice. The stratified Hazard ratio was based on Cox regression model including treatment arm as a covariate and stratified by pooled geographic region (Asia vs. Rest of World), prior definitive therapy and Investigator choice of chemotherapy as strata. | |
| Comparison groups | Placebo + Chemotherapy v Tislelizumab + Chemotherapy |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 649 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[1] |
| Method | Stratified Log-rank Test |
| Parameter estimate | Stratified Hazard Ratio |
| Point estimate | 0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.8 |

Notes:

[1] - One-sided p-value estimated from log rank test stratified by pooled geographic region, prior definitive therapy and Investigator chemotherapy choice.

Secondary: Progression-Free Survival (PFS)

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

End point description:

PFS is defined as the time from the date of randomization to the date of first documentation of disease progression assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, or death, whichever occurred first. Median PFS was estimated using the Kaplan-Meier method.

Progressive disease is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, and an absolute increase of at least 5 mm, or unequivocal progression of existing nontarget lesions, or the appearance of 1 or more new lesions.

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

End point timeframe:

From randomization to the primary analysis cutoff date of 28 February 2022; maximum time on follow-up was 3 years and 2 months.

| End point values | Tislelizumab + Chemotherapy | Placebo + Chemotherapy | | |
|----------------------------------|-----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 323 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.3 (6.9 to 8.3) | 5.6 (4.9 to 6.0) | | |

Statistical analyses

| | |
|----------------------------|-----------------|
| Statistical analysis title | Analysis of PFS |
|----------------------------|-----------------|

Statistical analysis description:

The stratified Hazard ratio was based on Cox regression model including treatment arm as a covariate and stratified by pooled geographic region (Asia vs. Rest of World), prior definitive therapy and Investigator choice of chemotherapy as strata.

| | |
|-------------------|--|
| Comparison groups | Tislelizumab + Chemotherapy v Placebo + Chemotherapy |
|-------------------|--|

| | |
|---|--------------------------|
| Number of subjects included in analysis | 649 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[2] |
| Method | Stratified Log-rank test |
| Parameter estimate | Stratified Hazard Ratio |
| Point estimate | 0.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 0.75 |

Notes:

[2] - One-sided p-value estimated from log rank test stratified by pooled geographic region, prior definitive therapy and Investigator chemotherapy choice.

Secondary: Objective Response Rate (ORR)

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|-----------------|-------------------------------|
| End point title | Objective Response Rate (ORR) |
|-----------------|-------------------------------|

End point description:

ORR is defined as the percentage of participants whose best overall response (BOR) was complete response (CR) or partial response (PR) assessed by the investigator per RECIST v1.1. Tumor assessments included computed tomography (CT) scans or magnetic resonance imaging (MRI), with preference for CT, of the neck, chest, and abdomen every 6 weeks for the first 48 weeks, then every 9 weeks after 48 weeks.

CR: Disappearance of all target and nontarget lesions with no new lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

PR: Disappearance of all target lesions with persistence of 1 or more nontarget lesion(s), no new lesions, and/or maintenance of tumor marker level above the normal limits, or, at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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

End point timeframe:

Response was assessed every 6 weeks for the first 48 weeks, then every 9 weeks thereafter; up to the primary analysis cutoff date of 28 February 2022; maximum time on follow-up was 3 years and 2 months.

| End point values | Tislelizumab + Chemotherapy | Placebo + Chemotherapy | | |
|-----------------------------------|-----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 323 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 63.5 (58.0 to 68.7) | 42.4 (37.0 to 48.0) | | |

Statistical analyses

| | |
|----------------------------|-----------------|
| Statistical analysis title | Analysis of ORR |
|----------------------------|-----------------|

Statistical analysis description:

The odds ratio was calculated using the Cochran-Mantel-Haenszel method, stratified by pooled geographic region, prior definitive therapy, and Investigator choice of chemotherapy.

| | |
|-------------------|--|
| Comparison groups | Tislelizumab + Chemotherapy v Placebo + Chemotherapy |
|-------------------|--|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 649 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.73 |
| upper limit | 3.27 |

Notes:

[3] - Two-sided Cochran-Mantel-Haenszel test was stratified by pooled geographic region, prior definitive therapy, and Investigator choice of chemotherapy.

Secondary: Overall Survival (OS) in Participants With a PD-L1 Score \geq 10%

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|---|---|
| End point title | Overall Survival (OS) in Participants With a PD-L1 Score \geq 10% |
| End point description: | |
| OS is defined as the time from the date of randomization until the date of death due to any cause. Median OS was estimated using the Kaplan-Meier method. The analysis included participants in the ITT Analysis Set with PD-L1 score \geq 10%. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization to the primary analysis cutoff date of 28 February 2022; maximum time on follow-up was 3 years and 2 months. | |

| End point values | Tislelizumab + Chemotherapy | Placebo + Chemotherapy | | |
|----------------------------------|-----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 107 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 16.6 (15.3 to 24.4) | 10.0 (8.6 to 13.3) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of OS in PD-L1 Score \geq 10% Subgroup |
| Statistical analysis description: | |
| Stratified Hazard ratio was based on Cox regression model including treatment arm as a covariate and stratified by pooled geographic region (Asia vs. Rest of World), prior definitive therapy and Investigator choice of chemotherapy as strata. | |
| Comparison groups | Tislelizumab + Chemotherapy v Placebo + Chemotherapy |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0029 ^[4] |
| Method | Stratified Log-rank test |
| Parameter estimate | Stratified Hazard Ratio |
| Point estimate | 0.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.44 |
| upper limit | 0.87 |

Notes:

[4] - One-sided p-value estimated from log rank test stratified by pooled geographic region, prior definitive therapy and Investigator chemotherapy choice.

Secondary: Duration of Response (DOR)

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|--|----------------------------|
| End point title | Duration of Response (DOR) |
| End point description: | |
| DOR is defined as the time from the first determination of an objective response until the first documentation of progression assessed by the investigator per RECIST v1.1 or death, whichever occurred first. Median DOR was estimated using the Kaplan-Meier method. | |
| The analysis includes participants in the ITT Analysis Set with an objective response. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization to the primary analysis cutoff date of 28 February 2022; maximum time on follow-up was 3 years and 2 months. | |

| End point values | Tislelizumab + Chemotherapy | Placebo + Chemotherapy | | |
|----------------------------------|-----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 207 | 137 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.1 (6.1 to 8.1) | 5.7 (4.4 to 7.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Oesophageal Cancer 18 Question Module (QLQ-OES18) Dysphagia, Eating, Reflux, Pain, and Index Scores

| | |
|-----------------|--|
| End point title | Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Oesophageal Cancer 18 Question Module (QLQ-OES18) Dysphagia, Eating, Reflux, Pain, and Index Scores |
|-----------------|--|

End point description:

The EORTC-QLQ-OES18 is the specific esophageal symptoms module of the QLQ-C30. QLQ-OES18 is comprised of 18 questions grouped into 4 multi-item subscales: Dysphagia (3 items), Eating (4 items), Reflux (2 items), and Pain (3 items) and 6 single item subscales (trouble swallowing saliva, choking, dry

mouth, taste, coughing, and talking). Participants indicate the extent to which they have experienced symptoms on a scale from 1 (Not at all) to 4 (Very much). Scores are calculated as the average of the items that contribute to the scale, then transformed to a scale from 0 to 100. The OES18 index score is calculated as the average of the 4 multi-item subscales and 6 single-item subscales. Higher scores indicate a higher level of symptomatology or problems.

The analysis includes participants in the ITT Analysis Set who completed the EORTC QLQ-OES18 at Baseline and at least one post-baseline measurement.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Cycle 6 (Week 15) | |

| End point values | Tislelizumab + Chemotherapy | Placebo + Chemotherapy | | |
|--|-----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 310 | 309 | | |
| Units: score on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Dysphagia | -0.5 (-4.7 to 3.7) | -4.9 (-9.4 to -0.5) | | |
| Eating | -0.9 (-3.1 to 1.3) | -1.5 (-3.8 to 0.9) | | |
| Reflux | -1.3 (-3.2 to 0.7) | 0.2 (-1.9 to 2.2) | | |
| Pain | -5.2 (-6.7 to -3.7) | -3.3 (-4.9 to -1.8) | | |
| Index Score | -1.0 (-2.2 to 0.3) | -0.6 (-1.9 to 0.7) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of EORTC QLQ-OES18 Dysphagia Score |
| Statistical analysis description: | |
| Analysis of Change from Baseline in EORTC QLQ-OES18 Dysphagia Score at Cycle 6 based on a mixed effect model analysis with QLQ-OES18 scores until Cycle 18 as the response variable, and treatment by study visit interaction, Baseline mean score, and randomization stratification factors as covariates. | |
| Comparison groups | Tislelizumab + Chemotherapy v Placebo + Chemotherapy |
| Number of subjects included in analysis | 619 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1372 ^[5] |
| Method | Mixed models analysis |
| Parameter estimate | Least Squares (LS) Mean Difference |
| Point estimate | 4.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4 |
| upper limit | 10.3 |

Notes:

[5] - Two-sided p-value estimated from a mixed effect model.

| Statistical analysis title | Analysis of EORTC QLQ-OES18 Eating Score |
|---|--|
| Statistical analysis description: Analysis of Change from Baseline in EORTC QLQ-OES18 Eating Score at Cycle 6 based on a mixed effect model analysis with QLQ-OES18 scores until Cycle 18 as the response variable, and treatment by study visit interaction, Baseline mean score, and randomization stratification factors as covariates. | |
| Comparison groups | Tislelizumab + Chemotherapy v Placebo + Chemotherapy |
| Number of subjects included in analysis | 619 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.713 ^[6] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | 3.7 |

Notes:

[6] - Two-sided p-value estimated from a mixed effect model.

| Statistical analysis title | Analysis of EORTC QLQ-OES18 Reflux Score |
|---|--|
| Statistical analysis description: Analysis of Change from Baseline in EORTC QLQ-OES18 Reflux Score at Cycle 6 based on a mixed effect model analysis with QLQ-OES18 scores until Cycle 18 as the response variable, and treatment by study visit interaction, Baseline mean score, and randomization stratification factors as covariates. | |
| Comparison groups | Tislelizumab + Chemotherapy v Placebo + Chemotherapy |
| Number of subjects included in analysis | 619 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3001 ^[7] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.1 |
| upper limit | 1.3 |

Notes:

[7] - Two-sided p-value estimated from a mixed effect model.

| Statistical analysis title | Analysis of EORTC QLQ-OES18 Pain Score |
|---|--|
| Statistical analysis description: Analysis of Change from Baseline in EORTC QLQ-OES18 Pain Score at Cycle 6 based on a mixed effect model analysis with QLQ-OES18 scores until Cycle 18 as the response variable, and treatment by study visit interaction, Baseline mean score, and randomization stratification factors as covariates. | |
| Comparison groups | Tislelizumab + Chemotherapy v Placebo + Chemotherapy |

| | |
|---|--------------------|
| Number of subjects included in analysis | 619 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.9 |
| upper limit | 0.2 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Analysis of EORTC QLQ-OES18 Index Score |
|-----------------------------------|---|

Statistical analysis description:

Analysis of Change from Baseline in EORTC QLQ-OES18 Index Score at Cycle 6 based on a mixed effect model analysis with QLQ-OES18 scores until Cycle 18 as the response variable, and treatment by study visit interaction, Baseline mean score, and randomization stratification factors as covariates.

| | |
|---|--|
| Comparison groups | Tislelizumab + Chemotherapy v Placebo + Chemotherapy |
| Number of subjects included in analysis | 619 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.1 |
| upper limit | 1.4 |

Secondary: Change From Baseline in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) Global Health Status/Quality of Life (GHS/QoL) and Physical Functioning Scales

| | |
|-----------------|---|
| End point title | Change From Baseline in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) Global Health Status/Quality of Life (GHS/QoL) and Physical Functioning Scales |
|-----------------|---|

End point description:

The EORTC QLQ-30 contains 30 questions that incorporate 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The participant answers questions about their health during the past week. There are 28 questions answered on a 4-point scale where 1 = Not at all (best) and 4 = Very Much (worst) and 2 global health quality of life (QOL) questions answered on a 7-point scale where 1 = Very poor and 7 = Excellent. Raw scores are transformed to a 0 to 100 scale via linear transformation. Higher scores in GHS and functional scales indicate better quality of life.

The analysis includes participants in the ITT Analysis Set who completed the EORTC QLQ-C30 at Baseline and at least one post-baseline measurement.

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

End point timeframe:

Baseline, Cycle 6 (Week 15)

| End point values | Tislelizumab + Chemotherapy | Placebo + Chemotherapy | | |
|--|--------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 310 | 309 | | |
| Units: score on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Global Health Status/QoL | -0.3 (-2.3 to 1.8) | -3.6 (-5.8 to -1.4) | | |
| Physical Functioning | -4.8 (-6.6 to -3.0) | -7.3 (-9.2 to -5.4) | | |

Statistical analyses

| Statistical analysis title | Analysis of EORTC QLQ-C30 GHS/QoL Score |
|---|--|
| Statistical analysis description: | |
| Analysis of Change from Baseline in Global Health Status/QoL at Cycle 6 based on a mixed effect model analysis, with QLQ-C30 scores until Cycle 18 as the response variable, and treatment by study visit interaction, Baseline mean score, and randomization stratification factors as covariates. | |
| Comparison groups | Tislelizumab + Chemotherapy v Placebo + Chemotherapy |
| Number of subjects included in analysis | 619 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | LS Mean Difference |
| Point estimate | 3.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 6.2 |

| Statistical analysis title | Analysis of EORTC QLQ-C30 Physical Functioning |
|---|--|
| Statistical analysis description: | |
| Analysis of Change from Baseline in Physical Functioning at Cycle 6 based on a mixed effect model analysis, with QLQ-C30 scores until cycle 18 as the response variable, and treatment by study visit interaction, Baseline mean score, and randomization stratification factors as covariates. | |
| Comparison groups | Tislelizumab + Chemotherapy v Placebo + Chemotherapy |
| Number of subjects included in analysis | 619 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | LS Mean Difference |
| Point estimate | 2.6 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 5.1 |

Secondary: Change From Baseline in EORTC QLQ-C30 Fatigue Scale

| | |
|-----------------|---|
| End point title | Change From Baseline in EORTC QLQ-C30 Fatigue Scale |
|-----------------|---|

End point description:

The EORTC QLQ-30 contains 30 questions that incorporate 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The participant answers questions about their health during the past week. There are 28 questions answered on a 4-point scale where 1 = Not at all (best) and 4 = Very Much (worst) and 2 global health quality of life (QOL) questions answered on a 7-point scale where 1 = Very poor and 7 = Excellent. Raw scores are transformed to a 0 to 100 scale via linear transformation. The fatigue symptom scale includes 3 items and ranges from 0 to 100, where higher scores indicate a higher level of symptoms.

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

End point timeframe:

Baseline, Cycle 6 (Week 15)

| End point values | Tislelizumab + Chemotherapy | Placebo + Chemotherapy | | |
|--|--------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 310 | 309 | | |
| Units: score on a scale | | | | |
| least squares mean (confidence interval 95%) | 8.0 (5.7 to 10.4) | 9.4 (6.9 to 11.9) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Analysis of EORTC QLQ-C30 Fatigue Scale |
|----------------------------|---|

Statistical analysis description:

Analysis of Change from Baseline in Fatigue at Cycle 6 based on a mixed effect model analysis with QLQ-C30 scores until Cycle 18 as the response variable, and treatment by study visit interaction, Baseline mean score, and randomization stratification factors as covariates.

| | |
|---|--|
| Comparison groups | Tislelizumab + Chemotherapy v Placebo + Chemotherapy |
| Number of subjects included in analysis | 619 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.4 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.7 |
| upper limit | 1.9 |

Secondary: Change From Baseline in European Quality of Life 5-Dimension 5-Level (EQ-5D-5L) Visual Analog Scale (VAS)

| | |
|-----------------|---|
| End point title | Change From Baseline in European Quality of Life 5-Dimension 5-Level (EQ-5D-5L) Visual Analog Scale (VAS) |
|-----------------|---|

End point description:

The EQ-5D-5L measures health outcomes using a VAS to record a participant's self-rated health on a scale from 0 to 100, where 100 is 'the best health you can imagine' and 0 is 'the worst health you can imagine.' A higher score indicates better health outcomes.

The analysis includes participants in the ITT Analysis Set with EQ-5D-5L measurement at both Baseline and Cycle 6.

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

End point timeframe:

Baseline, Cycle 6 (Week 15)

| End point values | Tislelizumab + Chemotherapy | Placebo + Chemotherapy | | |
|--------------------------------------|--------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 221 | 196 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | -1.1 (± 15.82) | -3.1 (± 14.01) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Treatment-emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Number of Participants Experiencing Treatment-emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) |
|-----------------|---|

End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drugs, whether related to study drugs or not.

An SAE is any untoward medical occurrence that, at any dose met any of the following criteria:

- Resulted in death.
- Was life-threatening.
- Required hospitalization or prolongation of existing hospitalization.
- Resulted in disability/incapacity.
- Was a congenital anomaly/birth defect.
- Was considered a significant medical AE by the Investigator based on medical judgement.

The Safety Analysis Set included all participants who received at least 1 dose of study drug.

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

End point timeframe:

From first dose of study drug up to 30 days after last dose; maximum time on treatment was 63.5 months.

| End point values | Tislelizumab + Chemotherapy | Placebo + Chemotherapy | | |
|----------------------------------|--------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 324 | 321 | | |
| Units: participants | | | | |
| Treatment-emergent adverse event | 323 | 319 | | |
| Serious adverse events | 160 | 128 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to 30 days after last dose, maximum time on treatment was 63.5 months.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 24 |

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Placebo + Chemotherapy |
|-----------------------|------------------------|

Reporting group description:

Participants received placebo administered IV on Day 1 of each 3-week treatment cycle together with an investigator-chosen chemotherapy doublet until unacceptable toxicity, disease progression or withdrawal for other reasons.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Tisnelizumab + Chemotherapy |
|-----------------------|-----------------------------|

Reporting group description:

Participants received tisnelizumab 200 mg administered intravenously on Day 1 of each 3-week treatment cycle together with an investigator-chosen chemotherapy doublet until unacceptable toxicity, disease progression or withdrawal for other reasons.

| Serious adverse events | Placebo + Chemotherapy | Tisnelizumab + Chemotherapy | |
|---|---------------------------|--------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 128 / 321 (39.88%) | 160 / 324 (49.38%) | |
| number of deaths (all causes) | 267 | 250 | |
| number of deaths resulting from adverse events | 17 | 16 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Invasive lobular breast carcinoma subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myeloproliferative neoplasm subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour associated fever subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Venous thrombosis limb subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism venous subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension subjects affected / exposed | 1 / 321 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iliac artery occlusion | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| 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 | | | |
| Accidental death | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest discomfort | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 4 / 321 (1.25%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 2 / 4 | 0 / 2 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 4 / 321 (1.25%) | 6 / 324 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 5 / 324 (1.54%) | |
| occurrences causally related to treatment / all | 3 / 3 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| 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 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (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 | 1 / 321 (0.31%) | 4 / 324 (1.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oesophagobronchial fistula | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acquired tracheo-oesophageal fistula | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asphyxia | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Immune-mediated lung disease | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 4 / 321 (1.25%) | 6 / 324 (1.85%) | |
| occurrences causally related to treatment / all | 3 / 4 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 4 / 321 (1.25%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | |
| Stridor | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 321 (1.25%) | 4 / 324 (1.23%) | |
| occurrences causally related to treatment / all | 1 / 6 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mutism | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| C-reactive protein increased subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 4 / 324 (1.23%) | |
| occurrences causally related to treatment / all | 3 / 3 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prohormone brain natriuretic peptide increased | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Anastomotic stenosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oropharyngeal stenosis | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic intracranial haemorrhage | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Unintentional medical device removal | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular access site haematoma | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Arteriosclerosis coronary artery | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Prinzmetal angina | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain injury | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebral infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant spinal cord compression | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 321 (1.87%) | 6 / 324 (1.85%) | |
| occurrences causally related to treatment / all | 4 / 6 | 7 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 4 / 321 (1.25%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 5 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelosuppression | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 7 / 321 (2.18%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 8 / 8 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 5 / 321 (1.56%) | 5 / 324 (1.54%) | |
| occurrences causally related to treatment / all | 5 / 5 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Sudden hearing loss | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Oesophageal obstruction | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 4 / 324 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|------------------|--|
| Constipation | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 7 / 324 (2.16%) | |
| occurrences causally related to treatment / all | 2 / 3 | 6 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 8 / 321 (2.49%) | 17 / 324 (5.25%) | |
| occurrences causally related to treatment / all | 0 / 8 | 1 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric perforation | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Ileus | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus paralytic | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 5 / 324 (1.54%) | |
| occurrences causally related to treatment / all | 3 / 3 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal dysplasia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal fistula | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal haemorrhage | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal perforation | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 5 / 324 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 4 / 324 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Vomiting | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 5 / 321 (1.56%) | 7 / 324 (2.16%) | |
| occurrences causally related to treatment / all | 4 / 5 | 5 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 7 / 324 (2.16%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune-mediated hepatitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 321 (0.00%) | 2 / 324 (0.62%) | |
| 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 | | | |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eczema | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erythema | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| 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 / 321 (0.00%) | 6 / 324 (1.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal injury | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal tubular dysfunction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hypopituitarism | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adrenocorticotrophic hormone deficiency | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Immune-mediated arthritis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myositis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Synovitis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess neck | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain abscess | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Carbuncle | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium colitis | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile infection | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic infection | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 23 / 321 (7.17%) | 19 / 324 (5.86%) | |
| occurrences causally related to treatment / all | 9 / 23 | 9 / 21 | |
| deaths causally related to treatment / all | 1 / 4 | 0 / 1 | |
| Post procedural pneumonia | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Rash pustular | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 4 / 324 (1.23%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Subcutaneous abscess | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethritis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 6 / 324 (1.85%) | |
| occurrences causally related to treatment / all | 2 / 3 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Hypercalcaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 321 (0.62%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 4 / 321 (1.25%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 3 / 4 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 321 (0.62%) | 6 / 324 (1.85%) | |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 321 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 321 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | Placebo + Chemotherapy | Tiselizumab + Chemotherapy | |
|---|-----------------------------------|---------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 314 / 321 (97.82%) | 321 / 324 (99.07%) | |
| Vascular disorders | | | |
| Phlebitis | | | |
| subjects affected / exposed | 10 / 321 (3.12%) | 7 / 324 (2.16%) | |
| occurrences (all) | 10 | 7 | |
| Hypertension | | | |
| subjects affected / exposed | 17 / 321 (5.30%) | 21 / 324 (6.48%) | |
| occurrences (all) | 24 | 29 | |
| Hypotension | | | |
| subjects affected / exposed | 5 / 321 (1.56%) | 14 / 324 (4.32%) | |
| occurrences (all) | 5 | 19 | |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 4 / 321 (1.25%) | 13 / 324 (4.01%) | |
| occurrences (all) | 4 | 14 | |
| Fatigue | | | |
| subjects affected / exposed | 55 / 321 (17.13%) | 64 / 324 (19.75%) | |
| occurrences (all) | 77 | 84 | |
| Malaise | | | |
| subjects affected / exposed | 51 / 321 (15.89%) | 40 / 324 (12.35%) | |
| occurrences (all) | 70 | 77 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 11 / 321 (3.43%) | 11 / 324 (3.40%) | |
| occurrences (all) | 14 | 16 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 12 / 321 (3.74%) | 14 / 324 (4.32%) | |
| occurrences (all) | 30 | 17 | |
| Pyrexia | | | |
| subjects affected / exposed | 38 / 321 (11.84%) | 54 / 324 (16.67%) | |
| occurrences (all) | 46 | 80 | |
| Asthenia | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 46 / 321 (14.33%) 55 | 42 / 324 (12.96%) 55 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 38 / 321 (11.84%) | 51 / 324 (15.74%) | |
| occurrences (all) | 45 | 62 | |
| Dysphonia | | | |
| subjects affected / exposed | 11 / 321 (3.43%) | 5 / 324 (1.54%) | |
| occurrences (all) | 11 | 5 | |
| Dyspnoea | | | |
| subjects affected / exposed | 14 / 321 (4.36%) | 23 / 324 (7.10%) | |
| occurrences (all) | 16 | 24 | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 10 / 324 (3.09%) | |
| occurrences (all) | 3 | 11 | |
| Hiccups | | | |
| subjects affected / exposed | 28 / 321 (8.72%) | 23 / 324 (7.10%) | |
| occurrences (all) | 47 | 35 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 4 / 321 (1.25%) | 19 / 324 (5.86%) | |
| occurrences (all) | 4 | 20 | |
| Pneumonitis | | | |
| subjects affected / exposed | 6 / 321 (1.87%) | 15 / 324 (4.63%) | |
| occurrences (all) | 6 | 16 | |
| Productive cough | | | |
| subjects affected / exposed | 18 / 321 (5.61%) | 25 / 324 (7.72%) | |
| occurrences (all) | 22 | 27 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 26 / 321 (8.10%) | 30 / 324 (9.26%) | |
| occurrences (all) | 34 | 36 | |
| Investigations | | | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 9 / 321 (2.80%) | 18 / 324 (5.56%) | |
| occurrences (all) | 13 | 24 | |
| Alanine aminotransferase increased | | | |

| | | |
|--|-------------------|-------------------|
| subjects affected / exposed | 42 / 321 (13.08%) | 49 / 324 (15.12%) |
| occurrences (all) | 61 | 76 |
| Amylase increased | | |
| subjects affected / exposed | 19 / 321 (5.92%) | 22 / 324 (6.79%) |
| occurrences (all) | 27 | 43 |
| Aspartate aminotransferase increased | | |
| subjects affected / exposed | 37 / 321 (11.53%) | 51 / 324 (15.74%) |
| occurrences (all) | 57 | 86 |
| Blood alkaline phosphatase increased | | |
| subjects affected / exposed | 15 / 321 (4.67%) | 18 / 324 (5.56%) |
| occurrences (all) | 20 | 28 |
| Blood bilirubin increased | | |
| subjects affected / exposed | 27 / 321 (8.41%) | 27 / 324 (8.33%) |
| occurrences (all) | 44 | 40 |
| Blood creatine phosphokinase increased | | |
| subjects affected / exposed | 8 / 321 (2.49%) | 13 / 324 (4.01%) |
| occurrences (all) | 16 | 26 |
| Blood creatinine increased | | |
| subjects affected / exposed | 30 / 321 (9.35%) | 47 / 324 (14.51%) |
| occurrences (all) | 73 | 83 |
| Blood urea increased | | |
| subjects affected / exposed | 16 / 321 (4.98%) | 24 / 324 (7.41%) |
| occurrences (all) | 32 | 51 |
| Gamma-glutamyltransferase increased | | |
| subjects affected / exposed | 17 / 321 (5.30%) | 16 / 324 (4.94%) |
| occurrences (all) | 21 | 23 |
| Lipase increased | | |
| subjects affected / exposed | 17 / 321 (5.30%) | 18 / 324 (5.56%) |
| occurrences (all) | 25 | 24 |
| Lymphocyte count decreased | | |
| subjects affected / exposed | 28 / 321 (8.72%) | 23 / 324 (7.10%) |
| occurrences (all) | 65 | 57 |
| Neutrophil count decreased | | |

| | | | |
|----------------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 155 / 321 (48.29%) | 153 / 324 (47.22%) | |
| occurrences (all) | 486 | 497 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 55 / 321 (17.13%) | 62 / 324 (19.14%) | |
| occurrences (all) | 111 | 121 | |
| Weight decreased | | | |
| subjects affected / exposed | 91 / 321 (28.35%) | 97 / 324 (29.94%) | |
| occurrences (all) | 112 | 125 | |
| Weight increased | | | |
| subjects affected / exposed | 13 / 321 (4.05%) | 29 / 324 (8.95%) | |
| occurrences (all) | 13 | 39 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 157 / 321 (48.91%) | 143 / 324 (44.14%) | |
| occurrences (all) | 520 | 487 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 17 / 321 (5.30%) | 16 / 324 (4.94%) | |
| occurrences (all) | 23 | 18 | |
| Dysgeusia | | | |
| subjects affected / exposed | 11 / 321 (3.43%) | 12 / 324 (3.70%) | |
| occurrences (all) | 13 | 14 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 40 / 321 (12.46%) | 34 / 324 (10.49%) | |
| occurrences (all) | 44 | 35 | |
| Neurotoxicity | | | |
| subjects affected / exposed | 11 / 321 (3.43%) | 16 / 324 (4.94%) | |
| occurrences (all) | 12 | 19 | |
| Paraesthesia | | | |
| subjects affected / exposed | 8 / 321 (2.49%) | 15 / 324 (4.63%) | |
| occurrences (all) | 8 | 17 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 62 / 321 (19.31%) | 74 / 324 (22.84%) | |
| occurrences (all) | 81 | 82 | |
| Headache | | | |
| subjects affected / exposed | 16 / 321 (4.98%) | 18 / 324 (5.56%) | |
| occurrences (all) | 16 | 22 | |

| | | | |
|--------------------------------------|--------------------|--------------------|--|
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 28 / 321 (8.72%) | 34 / 324 (10.49%) | |
| occurrences (all) | 87 | 86 | |
| Coagulopathy | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 13 / 324 (4.01%) | |
| occurrences (all) | 3 | 15 | |
| Anaemia | | | |
| subjects affected / exposed | 180 / 321 (56.07%) | 193 / 324 (59.57%) | |
| occurrences (all) | 322 | 343 | |
| Neutropenia | | | |
| subjects affected / exposed | 45 / 321 (14.02%) | 54 / 324 (16.67%) | |
| occurrences (all) | 148 | 122 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 24 / 321 (7.48%) | 29 / 324 (8.95%) | |
| occurrences (all) | 36 | 43 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 13 / 321 (4.05%) | 15 / 324 (4.63%) | |
| occurrences (all) | 20 | 19 | |
| Constipation | | | |
| subjects affected / exposed | 101 / 321 (31.46%) | 102 / 324 (31.48%) | |
| occurrences (all) | 130 | 141 | |
| Diarrhoea | | | |
| subjects affected / exposed | 76 / 321 (23.68%) | 88 / 324 (27.16%) | |
| occurrences (all) | 118 | 124 | |
| Dyspepsia | | | |
| subjects affected / exposed | 8 / 321 (2.49%) | 13 / 324 (4.01%) | |
| occurrences (all) | 8 | 21 | |
| Dysphagia | | | |
| subjects affected / exposed | 29 / 321 (9.03%) | 32 / 324 (9.88%) | |
| occurrences (all) | 30 | 41 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 15 / 321 (4.67%) | 23 / 324 (7.10%) | |
| occurrences (all) | 17 | 26 | |
| Nausea | | | |

| | | | |
|---|--------------------|--------------------|--|
| subjects affected / exposed | 136 / 321 (42.37%) | 122 / 324 (37.65%) | |
| occurrences (all) | 229 | 203 | |
| Stomatitis | | | |
| subjects affected / exposed | 48 / 321 (14.95%) | 60 / 324 (18.52%) | |
| occurrences (all) | 67 | 113 | |
| Vomiting | | | |
| subjects affected / exposed | 86 / 321 (26.79%) | 68 / 324 (20.99%) | |
| occurrences (all) | 145 | 112 | |
| Abdominal pain | | | |
| subjects affected / exposed | 13 / 321 (4.05%) | 25 / 324 (7.72%) | |
| occurrences (all) | 17 | 26 | |
| Abdominal distension | | | |
| subjects affected / exposed | 14 / 321 (4.36%) | 17 / 324 (5.25%) | |
| occurrences (all) | 19 | 29 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 63 / 321 (19.63%) | 61 / 324 (18.83%) | |
| occurrences (all) | 63 | 61 | |
| Dry skin | | | |
| subjects affected / exposed | 7 / 321 (2.18%) | 12 / 324 (3.70%) | |
| occurrences (all) | 7 | 16 | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 14 / 321 (4.36%) | 14 / 324 (4.32%) | |
| occurrences (all) | 16 | 17 | |
| Pruritus | | | |
| subjects affected / exposed | 21 / 321 (6.54%) | 45 / 324 (13.89%) | |
| occurrences (all) | 27 | 56 | |
| Rash | | | |
| subjects affected / exposed | 24 / 321 (7.48%) | 38 / 324 (11.73%) | |
| occurrences (all) | 30 | 53 | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 15 / 321 (4.67%) | 33 / 324 (10.19%) | |
| occurrences (all) | 21 | 35 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|------------------------------------|--------------------|--------------------|--|
| Arthralgia | | | |
| subjects affected / exposed | 32 / 321 (9.97%) | 30 / 324 (9.26%) | |
| occurrences (all) | 45 | 37 | |
| Back pain | | | |
| subjects affected / exposed | 20 / 321 (6.23%) | 23 / 324 (7.10%) | |
| occurrences (all) | 25 | 26 | |
| Muscular weakness | | | |
| subjects affected / exposed | 7 / 321 (2.18%) | 10 / 324 (3.09%) | |
| occurrences (all) | 8 | 12 | |
| Myalgia | | | |
| subjects affected / exposed | 22 / 321 (6.85%) | 28 / 324 (8.64%) | |
| occurrences (all) | 29 | 42 | |
| Pain in extremity | | | |
| subjects affected / exposed | 29 / 321 (9.03%) | 27 / 324 (8.33%) | |
| occurrences (all) | 36 | 37 | |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 3 / 321 (0.93%) | 10 / 324 (3.09%) | |
| occurrences (all) | 3 | 11 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 6 / 321 (1.87%) | 10 / 324 (3.09%) | |
| occurrences (all) | 6 | 11 | |
| Pneumonia | | | |
| subjects affected / exposed | 14 / 321 (4.36%) | 26 / 324 (8.02%) | |
| occurrences (all) | 15 | 28 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 17 / 321 (5.30%) | 29 / 324 (8.95%) | |
| occurrences (all) | 19 | 36 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 124 / 321 (38.63%) | 142 / 324 (43.83%) | |
| occurrences (all) | 195 | 205 | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 7 / 321 (2.18%) | 13 / 324 (4.01%) | |
| occurrences (all) | 21 | 27 | |
| Hyperglycaemia | | | |

| | | |
|-----------------------------|-------------------|-------------------|
| subjects affected / exposed | 26 / 321 (8.10%) | 33 / 324 (10.19%) |
| occurrences (all) | 35 | 48 |
| Hyperkalaemia | | |
| subjects affected / exposed | 17 / 321 (5.30%) | 22 / 324 (6.79%) |
| occurrences (all) | 33 | 33 |
| Hypertriglyceridaemia | | |
| subjects affected / exposed | 13 / 321 (4.05%) | 16 / 324 (4.94%) |
| occurrences (all) | 28 | 37 |
| Hyperuricaemia | | |
| subjects affected / exposed | 25 / 321 (7.79%) | 27 / 324 (8.33%) |
| occurrences (all) | 61 | 78 |
| Hypoalbuminaemia | | |
| subjects affected / exposed | 60 / 321 (18.69%) | 75 / 324 (23.15%) |
| occurrences (all) | 115 | 157 |
| Hypocalcaemia | | |
| subjects affected / exposed | 17 / 321 (5.30%) | 20 / 324 (6.17%) |
| occurrences (all) | 28 | 28 |
| Hypochloraemia | | |
| subjects affected / exposed | 31 / 321 (9.66%) | 37 / 324 (11.42%) |
| occurrences (all) | 52 | 64 |
| Hypokalaemia | | |
| subjects affected / exposed | 54 / 321 (16.82%) | 64 / 324 (19.75%) |
| occurrences (all) | 83 | 105 |
| Hypomagnesaemia | | |
| subjects affected / exposed | 29 / 321 (9.03%) | 31 / 324 (9.57%) |
| occurrences (all) | 41 | 68 |
| Hyponatraemia | | |
| subjects affected / exposed | 58 / 321 (18.07%) | 73 / 324 (22.53%) |
| occurrences (all) | 99 | 129 |
| Hypophosphataemia | | |
| subjects affected / exposed | 15 / 321 (4.67%) | 16 / 324 (4.94%) |
| occurrences (all) | 24 | 22 |
| Hypoproteinaemia | | |
| subjects affected / exposed | 12 / 321 (3.74%) | 14 / 324 (4.32%) |
| occurrences (all) | 21 | 18 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 19 September 2018 | <p>Key changes included:</p> <ul style="list-style-type: none">• Added a third stratification factor of investigator choice of chemotherapy for randomization.• Revised inclusion criterion to only allow histologically confirmed diagnosis of ESCC but not either histologically or cytologically confirmed ones.• Revised inclusion criteria for patients with HBV and deleted HCV-associated criteria.• Added criteria to exclude patients who recurred after definitive surgery but still amenable to definitive radiation therapy and/or chemoradiotherapy.• Added enrollment guidelines and monitoring measures for Japanese patients prior to opening full enrollment in Japan.• Added treatment guidance that allowed platinum agent being cisplatin or oxaliplatin (except in China and Japan where oxaliplatin was not permitted) and being stopped after 6 cycles per site or investigator preference or per standard practice.• Added the dose delay or modification guidelines for oxaliplatin.• Added eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) assessed by an appropriate specialist for increased risks of ophthalmologic AEs after receiving PD-1 inhibitors.• Changed imaging of pelvis to imaging of neck, ie made neck a mandatory site for tumor assessment.• Added potential imAEs of myositis/rhabdomyolysis and myocarditis, including laboratory monitoring for these imAEs and evaluation and management guidelines.• Added the follow-up tumor assessment for patients who continued treatment beyond initial disease progression should be performed no more than 6 to 8 weeks after the initial assessment of radiographic disease progression per Regulatory Authorities' requirement. |
| 15 August 2019 | <p>Key changes included:</p> <ul style="list-style-type: none">• Added additional guidance for patients to take a pulmonary function test at screening.• Added 24 months as the treatment duration and the options of whether to keep on treatment when patients complete the 24 months of treatment.• Added new inclusion criterion "Have newly obtained or archival tissue sample available for biomarker assessment." to require mandatory collection of tumor tissue.• Clarified inclusion criteria to allow the enrollment of patients whose ESCC with adenocarcinoma differentiation < 5% of the viable tumor sample.• Revised exclusion criterion to exclude any patients who had chance to receive definitive surgery or was potentially curable with radiation therapy.• Updated the enrollment guidelines and monitoring measures for Japanese patients.• Revised the overdose definition for tislelizumab with detailed dose limit.• Added a table with the guidance on dose management including the recommended dose reduction level of each chemotherapy drug. |
| 25 May 2020 | <p>Key changes included:</p> <ul style="list-style-type: none">• Increased sample size from 480 to 622.• Added cardiac enzyme monitoring per the latest protocol template update.• Specified that nonserious AEs that were considered unequivocally due to disease progression should not be recorded, however if there was any uncertainty, it should be recorded as an AE. All SAEs and deaths regardless of relatedness to disease progression should be recorded and reported per the latest protocol template update. |

| | |
|---------------|---|
| 30 April 2021 | <p>Key changes included:</p> <ul style="list-style-type: none"> • Moved BIRC-assessed PFS from a dual primary objective/endpoint to an exploratory objective/endpoint. • Moved BIRC-assessed ORR and BIRC-assessed DOR from secondary endpoints to exploratory endpoints. • Added one secondary objective: OS in the PD-L1 score \geq 10% subgroup. • Adjusted the timing for the interim analyses of OS. • Defined PFS assessed by the investigator, OS in the PD-L1 score \geq 10% subgroup, ORR assessed by the investigator, and HRQoL for hierarchical sequential testing with alpha control. |
| 13 March 2024 | <p>Key changes included:</p> <ul style="list-style-type: none"> • Add description of unblinding and placebo discontinuation of the study after its interim analysis. • Added description of a rollover study so patients who may benefit from tislelizumab could be offered the option to continue treatment after study closeout. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported