



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
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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

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
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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
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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
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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
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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)
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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
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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
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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
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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)

End point title	Objective Response Rate (ORR)
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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
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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
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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
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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%

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)

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
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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
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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
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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
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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:	
<p>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.</p>	
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:	
<p>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.</p>	
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:	
<p>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.</p> <p>The analysis includes participants in the ITT Analysis Set with EQ-5D-5L measurement at both Baseline and Cycle 6.</p>	
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:	
<p>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.</p> <p>An SAE is any untoward medical occurrence that, at any dose met any of the following criteria:</p> <ul style="list-style-type: none"> - 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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Placebo + Chemotherapy
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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
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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