Clinical trial results:
A Randomized Phase III Study of Pembrolizumab Given Concomitantly With Chemoradiation and As Maintenance Therapy Versus Chemoradiation Alone in Subjects With Locally Advanced Head and Neck Squamous Cell Carcinoma (KEYNOTE-412)

Summary

EudraCT number	2016-003934-25
Trial protocol	DE GB ES NL AT PL CZ BE FR IT
Global end of trial date	21 August 2024

Results information

Result version number	v1 (current)
This version publication date	05 September 2025
First version publication date	05 September 2025

Trial information

Trial identification

Sponsor protocol code	3475-412

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03040999
WHO universal trial number (UTN)	-
Other trial identifiers	MSD: KEYNOTE-412

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.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	21 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2022
Global end of trial reached?	Yes
Global end of trial date	21 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine the efficacy and safety of pembrolizumab given concomitantly with chemoradiation (CRT) and as maintenance therapy versus placebo plus CRT in participants with locally advanced head and neck squamous cell carcinoma (LA HNSCC). The primary hypothesis is that pembrolizumab in combination with CRT is superior to placebo in combination with CRT with respect to event-free survival (EFS).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 April 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 39
Country: Number of subjects enrolled	Austria: 47
Country: Number of subjects enrolled	Belgium: 32
Country: Number of subjects enrolled	Brazil: 92
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Colombia: 24
Country: Number of subjects enrolled	Czechia: 24
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Spain: 45
Country: Number of subjects enrolled	France: 88
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Israel: 37
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Japan: 48
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Poland: 45
Country: Number of subjects enrolled	Türkiye: 45
Country: Number of subjects enrolled	Taiwan: 35

Country: Number of subjects enrolled	United States: 63
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	New Zealand: 3
Worldwide total number of subjects	804
EEA total number of subjects	348

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)	599
From 65 to 84 years	205
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled who had locally advanced (LA) head and neck squamous cell carcinoma (HNSCC) and were eligible for definitive chemoradiation therapy (CRT); had an Eastern Cooperative Oncology Group performance score of 0 or 1; had no distant metastases; and no active autoimmune disease or infection requiring systemic therapy.

Pre-assignment

Screening details:

A total of 1093 participants were screened, across 130 study sites in 21 countries.

Period 1

Period 1 title	Baseline Period (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	Pembrolizumab + CRT + Pembrolizumab

Arm description:

On Cycle 1 Day 1 (each cycle is 21 days), participants received a priming dose of 200 mg Pembrolizumab followed by 100 mg/m^2 Cisplatin PLUS 70 Gray (Gy) Radiotherapy (accelerated (AFX) or standard fractionation radiotherapy (SFX)) on Day 8 of Cycles 1, 2 and Cycle 3 (SFX RT regimen only). During CRT, participants received 2 doses of pembrolizumab (Day 1 of Cycles 2 and 3) and up to 3 cycles of Cisplatin (2 cycles during AFX and 3 cycles during SFX RT). Participants also received up to an additional 14 cycles of pembrolizumab alone as maintenance therapy for a total of 17 cycles of pembrolizumab (approximately 1 year). If cisplatin and/or radiation therapy was discontinued, the participant may continue on treatment with pembrolizumab.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	Keytruda®, MK-3475
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg Intravenous (IV) infusion on Day 1 of each 3-week (Q3W) cycle up to 17 doses (approximately 1 year). Each cycle is 21 days

Investigational medicinal product name	Standard Fractionation (SFX) Radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor
Routes of administration	Other use

Dosage and administration details:

70 Gy given in 35 fractions over 7 weeks

Investigational medicinal product name	Accelerated Fractionation (AFX) Radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor
Routes of administration	Other use

Dosage and administration details:

70 Gray (Gy) given in 35 fractions over 6 weeks

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mg/m^2 IV infusion on Cycle 1, Day 8; Cycle 2, Day 8; and Cycle 3, Day 8. Each cycle is 21 days

Arm title	Placebo + CRT + Placebo

Arm description:

On Cycle 1 Day 1 (each cycle is 21 days), participants received placebo followed by 100 mg/m^2 Cisplatin PLUS 70 Gray (Gy) Radiotherapy (accelerated (AFX) or standard fractionation radiotherapy (SFX)) on Day 8 of Cycles 1, 2 and Cycle 3 (SFX RT regimen only). During CRT, participants received 2 doses of placebo (Day 1 of Cycles 2 and 3) and up to 3 cycles of Cisplatin (2 cycles during AFX and 3 cycles during SFX RT). Participants also received up to an additional 14 cycles of placebo alone as maintenance therapy for a total of 17 cycles of placebo (approximately 1 year). If cisplatin and/or radiation therapy was discontinued, the participant may continue on treatment with placebo.

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

Dosage and administration details:

IV Infusion on Day 1 of each 3-week (Q3W) cycle
up to 17 doses (approximately 1 year). Each cycle is 21 days.

Investigational medicinal product name	Accelerated Fractionation (AFX) Radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor
Routes of administration	Other use

Dosage and administration details:

70 Gray (Gy) given in 35 fractions over 6 weeks

Investigational medicinal product name	Standard Fractionation (SFX) Radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor
Routes of administration	Other use

Dosage and administration details:

70 Gy given in 35 fractions over 7 weeks

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mg/m^2 IV infusion on Cycle 1, Day 8; Cycle 2, Day 8; and Cycle 3, Day 8. Each cycle is 21 days

Number of subjects in period 1	Pembrolizumab + CRT + Pembrolizumab	Placebo + CRT + Placebo
Started	402	402
Treated	398	398
Completed	233	213
Not completed	169	189
Physician decision	-	3
Death	155	171
Withdrawal by Subject	12	13
Lost to follow-up	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab + CRT + Pembrolizumab

Reporting group description:

On Cycle 1 Day 1 (each cycle is 21 days), participants received a priming dose of 200 mg Pembrolizumab followed by 100 mg/m^2 Cisplatin PLUS 70 Gray (Gy) Radiotherapy (accelerated (AFX) or standard fractionation radiotherapy (SFX)) on Day 8 of Cycles 1, 2 and Cycle 3 (SFX RT regimen only). During CRT, participants received 2 doses of pembrolizumab (Day 1 of Cycles 2 and 3) and up to 3 cycles of Cisplatin (2 cycles during AFX and 3 cycles during SFX RT). Participants also received up to an additional 14 cycles of pembrolizumab alone as maintenance therapy for a total of 17 cycles of pembrolizumab (approximately 1 year). If cisplatin and/or radiation therapy was discontinued, the participant may continue on treatment with pembrolizumab.

Reporting group title	Placebo + CRT + Placebo

Reporting group description:

On Cycle 1 Day 1 (each cycle is 21 days), participants received placebo followed by 100 mg/m^2 Cisplatin PLUS 70 Gray (Gy) Radiotherapy (accelerated (AFX) or standard fractionation radiotherapy (SFX)) on Day 8 of Cycles 1, 2 and Cycle 3 (SFX RT regimen only). During CRT, participants received 2 doses of placebo (Day 1 of Cycles 2 and 3) and up to 3 cycles of Cisplatin (2 cycles during AFX and 3 cycles during SFX RT). Participants also received up to an additional 14 cycles of placebo alone as maintenance therapy for a total of 17 cycles of placebo (approximately 1 year). If cisplatin and/or radiation therapy was discontinued, the participant may continue on treatment with placebo.

Reporting group values	Pembrolizumab + CRT + Pembrolizumab	Placebo + CRT + Placebo	Total
Number of subjects	402	402	804
Age Categorical Units: Participants			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	293	306	599
From 65-84 years	109	96	205
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	58.8	58.6	
standard deviation	± 9.0	± 7.8	-
Gender Categorical Units: Participants			
Female	71	73	144
Male	331	329	660
Race Units: Subjects			
American Indian Or Alaska Native	2	0	2
Asian	54	48	102
Black Or African American	10	11	21
Multiple	19	28	47

White	314	313	627
Missing	3	2	5
Ethnicity Units: Subjects			
Hispanic Or Latino	47	59	106
Not Hispanic Or Latino	324	312	636
Not Reported	25	26	51
Unknown	6	5	11
Human Papilloma Virus (HPV) Status			
Participants were assessed for HPV status using immunohistochemistry (IHC) analysis with CINtec® p16 histology assay. Positive p16 expression was defined as a strong and diffuse nuclear and cytoplasmic staining in 70% or more of the tumor cells.			
Units: Subjects			
Positive	109	104	213
Negative	293	298	591
Disease stage at baseline			
Disease status at baseline was done using the American Joint Committee on Cancer (AJCC) Staging manual for head and neck cancers. AJCC7 for patients enrolled before Jan 1, 2018, and AJCC8 for those enrolled on or after Jan 1, 2018. Stages progress from best (II) to worst prognosis (IVb). Stage II: Large tumor size and/or limited local spread; Stage III: Large tumor size and/or limited local spread and/or spread to neck lymph nodes (NLNs); Stage IVa: Moderately advanced locally and/or spread to NLNs; Stage IVb: Very advanced locally and/or spread to NLNs with extranodal extension.			
Units: Subjects			
AJCC7 III	8	11	19
AJCC7 IVA	61	58	119
AJCC7 IVB	12	14	26
AJCC8 II	0	1	1
AJCC8 III	132	125	257
AJCC8 IVA	146	152	298
AJCC8 IVB	43	41	84

End points

End points reporting groups

Reporting group title	Pembrolizumab + CRT + Pembrolizumab

Reporting group description:

On Cycle 1 Day 1 (each cycle is 21 days), participants received a priming dose of 200 mg Pembrolizumab followed by 100 mg/m^2 Cisplatin PLUS 70 Gray (Gy) Radiotherapy (accelerated (AFX) or standard fractionation radiotherapy (SFX)) on Day 8 of Cycles 1, 2 and Cycle 3 (SFX RT regimen only). During CRT, participants received 2 doses of pembrolizumab (Day 1 of Cycles 2 and 3) and up to 3 cycles of Cisplatin (2 cycles during AFX and 3 cycles during SFX RT). Participants also received up to an additional 14 cycles of pembrolizumab alone as maintenance therapy for a total of 17 cycles of pembrolizumab (approximately 1 year). If cisplatin and/or radiation therapy was discontinued, the participant may continue on treatment with pembrolizumab.

Reporting group title	Placebo + CRT + Placebo

Reporting group description:

On Cycle 1 Day 1 (each cycle is 21 days), participants received placebo followed by 100 mg/m^2 Cisplatin PLUS 70 Gray (Gy) Radiotherapy (accelerated (AFX) or standard fractionation radiotherapy (SFX)) on Day 8 of Cycles 1, 2 and Cycle 3 (SFX RT regimen only). During CRT, participants received 2 doses of placebo (Day 1 of Cycles 2 and 3) and up to 3 cycles of Cisplatin (2 cycles during AFX and 3 cycles during SFX RT). Participants also received up to an additional 14 cycles of placebo alone as maintenance therapy for a total of 17 cycles of placebo (approximately 1 year). If cisplatin and/or radiation therapy was discontinued, the participant may continue on treatment with placebo.

Primary: Event-free Survival (EFS)

End point title	Event-free Survival (EFS)

End point description:

EFS is the time from date of randomization to the date of first record of any of the following events: death due to any cause; progression per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by blinded independent central review (BICR) or biopsy as indicated for locoregional progression or recurrence or distant metastasis. As well as the first record of the following types of surgery: salvage surgery for persistent or residual disease at the primary tumor site requiring surgical removal when invasive cancer is present on final pathology; neck dissection or surgery (performed for clinical or radiological disease progression per RECIST 1.1) ≤ 20 weeks from end of CRT when invasive cancer is present; or neck dissection or surgery >20 weeks from end of CRT when invasive cancer is present. A value of 9999 indicates median and upper limit not reached due to insufficient number of participants with an event. Analysis population consists of all randomized participants.

End point type	Primary

End point timeframe:

Up to approximately 62 months

End point values	Pembrolizumab + CRT + Pembrolizumab	Placebo + CRT + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402	402		
Units: Months				
median (confidence interval 95%)	9999 (44.7 to 9999)	46.6 (27.5 to 9999)		

Statistical analyses

Statistical analysis title	EFS: Pembrolizumab + CRT Vs Placebo + CRT

Statistical analysis description:

Based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by HPV status and overall cancer stage.

Comparison groups	Pembrolizumab + CRT + Pembrolizumab v Placebo + CRT + Placebo
Number of subjects included in analysis	804
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0429 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.03

Notes:

[1] - P-value crossing boundary of 0.0242 required for statistical significance.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomization to the date of death due to any cause. Participants without documented death at the time of analysis were censored at the date the participant was last known to be alive. The non-parametric Kaplan-Meier method was used to estimate the survival curve in each treatment group. A value of 9999 indicates that median, upper limit, and lower limit were not reached due to insufficient number of participants with an event. Analysis population consists of all randomized participants.

End point type	Secondary

End point timeframe:

Up to approximately 88 months

End point values	Pembrolizumab + CRT + Pembrolizumab	Placebo + CRT + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402	402		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	OS: Pembrolizumab + CRT Vs Placebo + CRT +

Statistical analysis description:

Based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by HPV status and overall cancer stage.

Comparison groups	Pembrolizumab + CRT + Pembrolizumab v Placebo + CRT + Placebo
Number of subjects included in analysis	804
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1997
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.15

Secondary: Number of participants who experienced an Adverse Event (AE)

End point title	Number of participants who experienced an Adverse Event (AE)

End point description:

An AE was defined as any untoward medical occurrence in a participant administered study drug and which does not necessarily have to have a causal relationship with the study drug. An AE is any sign, symptom, disease, or worsening of preexisting condition temporally associated with study therapy and irrespective of causality to study therapy. The number of participants who experienced an AE is presented. Analysis population consists of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 88 months

End point values	Pembrolizumab + CRT + Pembrolizumab	Placebo + CRT + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	398		
Units: Number of Participants	398	397		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) Global Health Status (Item 29) Score

End point title	Change From Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life

	Questionnaire-Core 30 (EORTC QLQ-C30) Global Health Status (Item 29) Score

End point description:

The EORTC QLQ-C30 is a 30-item questionnaire developed to assess the quality of life (QoL) of cancer patients. For Global Health Status (GHS) (Item 29), participants are asked "How would you rate your overall health during the past week?" Individual items are scored on a 7-point (1=very poor to 7=excellent). Raw scores for each scale are standardized into a range of 0 to 100 by linear transformation, with a higher score indicating a better level of function and better overall GHS. A change from baseline of 10 points on the 100-point EORTC QLQ-C30 scale is considered as clinically relevant. Analysis population consists of participants with at least one patient reported outcome (PRO) assessment available for this specific endpoint and who had received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Baseline and up to Week 45

End point values	Pembrolizumab + CRT + Pembrolizumab	Placebo + CRT + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	392		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	1.93 (-0.12 to 3.99)	6.17 (4.10 to 8.23)		

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean

Statistical analysis description:

Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, time, treatment by time interaction, and stratification factors of HPV status and overall cancer stage.

Comparison groups	Pembrolizumab + CRT + Pembrolizumab v Placebo + CRT + Placebo
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0015 [2]
Method	cLDA
Parameter estimate	Hazard ratio (HR)
Point estimate	-4.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.85
upper limit	-1.63

Notes:

[2] - Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, time, treatment by time interaction, and stratification factors of HPV status and overall cancer stage.

Secondary: Change From Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck Questionnaire

(EORTC QLQ-H&N35) Swallowing Score

End point title	Change From Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck Questionnaire (EORTC QLQ-H&N35) Swallowing Score

End point description:

EORTC QLQ Head and Neck Questionnaire (H&N35) measures QoL in head and neck cancer (HNC) patients. It consists of 7 multi-item scales (pain in the mouth, problems with swallowing, senses, speech, social eating, social contact, and sexuality). Participant responses to the swallowing scale (Items 35-38) were scored on a 4-point scale (1=Not at all to 4=Very much). Raw scores were standardized by linear transformation so that scores ranged from 0 to 100, with a higher score indicating more problems. Change from baseline in swallowing was measured. A change from baseline of 10 points on the 100-point EORTC QLQ-H&N35 is considered as clinically relevant. Analysis population consists of participants with at least one PRO assessment available for this specific endpoint and who had received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Baseline and up to Week 45

End point values	Pembrolizumab + CRT + Pembrolizumab	Placebo + CRT + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	391		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-3.86 (-6.57 to -1.15)	-3.35 (-6.08 to -0.62)		

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean

Statistical analysis description:

Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, time, treatment by time interaction, and stratification factors of HPV status and overall cancer stage.

Comparison groups	Pembrolizumab + CRT + Pembrolizumab v Placebo + CRT + Placebo
Number of subjects included in analysis	784
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7719 [3]
Method	cLDA
Parameter estimate	Hazard ratio (HR)
Point estimate	-4.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.85
upper limit	-1.63

Notes:

[3] - Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, time, treatment by time interaction, and stratification factors of HPV status and overall cancer stage.

Secondary: Number of participants who discontinued study drug due to an AE

End point title	Number of participants who discontinued study drug due to an AE

End point description:

An AE was defined as any untoward medical occurrence in a participant administered study drug and which does not necessarily have to have a causal relationship with the study drug. An AE is any sign, symptom, disease, or worsening of preexisting condition temporally associated with study therapy and irrespective of causality to study therapy. The number of participants who discontinued study drug due to an AE is presented. Analysis population consists of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 15 months

End point values	Pembrolizumab + CRT + Pembrolizumab	Placebo + CRT + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	398		
Units: Number of Participants	163	132		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck Questionnaire (EORTC QLQ-H&N35) Speech score

End point title	Change From Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck Questionnaire (EORTC QLQ-H&N35) Speech score

End point description:

EORTC QLQ Head and Neck Questionnaire (H&N35) measures QoL in head and neck cancer (HNC) patients. It consists of 7 multi-item scales (pain in the mouth, problems with swallowing, senses, speech, social eating, social contact, and sexuality). Participant responses to the speech scale (Items 30-32) were scored on a 4-point scale (1=Not at all to 4=Very much). Raw scores were standardized by linear transformation so that scores ranged from 0 to 100, with a higher score indicating more problems. Change from baseline in speech was measured. A change from baseline of 10 points on the 100-point EORTC QLQ-H&N35 is considered as clinically relevant. Analysis population consists of participants with at least one PRO assessment available for this specific endpoint and who had received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Baseline and up to Week 45

End point values	Pembrolizumab + CRT + Pembrolizumab	Placebo + CRT + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	391		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-6.22 (-8.89 to -3.54)	-4.93 (-7.62 to -2.23)		

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean

Statistical analysis description:

Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, time, treatment by time interaction, and stratification factors of HPV status and overall cancer stage.

Comparison groups	Pembrolizumab + CRT + Pembrolizumab v Placebo + CRT + Placebo
Number of subjects included in analysis	784
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.45 [4]
Method	cLDA
Parameter estimate	Hazard ratio (HR)
Point estimate	-1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.64
upper limit	2.06

Notes:

[4] - Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, time, treatment by time interaction, and stratification factors of HPV status and overall cancer stage.

Secondary: Change From Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck Questionnaire (EORTC QLQ-H&N35) Pain Symptom Score

End point title	Change From Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck Questionnaire (EORTC QLQ-H&N35) Pain Symptom Score

End point description:

ORTC QLQ Head and Neck Questionnaire (H&N35) measures QoL in head and Neck Cancer (HNC) patients. It consists of 7 multi-item scales (pain in the mouth, problems with swallowing, senses, speech, social eating, social contact, and sexuality). Participant responses to the pain scale (Items 31-34) were scored on a 4-point scale (1=Not at all to 4=Very much). Raw scores were standardized by linear transformation so that scores ranged from 0 to 100, with a higher score indicating more problems. Change from baseline in pain symptoms was measured. A change from baseline of 10 points on the 100-point EORTC QLQ-H&N35 is considered as clinically relevant. Analysis population consists of participants with at least one PRO assessment available for this specific endpoint and who had received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Baseline and up to Week 45

End point values	Pembrolizumab + CRT + Pembrolizumab	Placebo + CRT + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	391		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-10.55 (-12.87 to -8.22)	-11.84 (-14.18 to -9.50)		

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean

Statistical analysis description:

Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, time, treatment by time interaction, and stratification factors of HPV status and overall cancer stage.

Comparison groups	Pembrolizumab + CRT + Pembrolizumab v Placebo + CRT + Placebo
Number of subjects included in analysis	784
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3524 [5]
Method	cLDA
Parameter estimate	Hazard ratio (HR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.43
upper limit	4.02

Notes:

[5] - Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, time, treatment by time interaction, and stratification factors of HPV status and overall cancer stage.

Secondary: Change From Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) Physical Functioning Score

End point title	Change From Baseline in European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) Physical Functioning Score

End point description:

The EORTC QLQ-C30 is a 30-item questionnaire developed to assess the quality of life (QoL) of cancer patients. Participant responded to 5 questions from the EORTC QLQ-C30 about their physical functioning scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores were standardized, so that scores range from 0 to 100, where a higher score indicates a better physical functioning. A change from baseline of 10 points on the 100-point scale is considered as clinically relevant. Analysis population consists of participants with at least one PRO assessment available for this

specific endpoint and who had received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Baseline and up to Week 45

End point values	Pembrolizumab + CRT + Pembrolizumab	Placebo + CRT + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	392		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-5.58 (-7.37 to -3.80)	-3.53 (-5.32 to -1.74)		

Statistical analyses

Statistical analysis title	Difference in LS Means

Statistical analysis description:

Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, time, treatment by time interaction, and stratification factors of HPV status and overall cancer stage

Comparison groups	Pembrolizumab + CRT + Pembrolizumab v Placebo + CRT + Placebo
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0963 [6]
Method	cLDA
Parameter estimate	Difference in LS Means
Point estimate	-2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.47
upper limit	0.37

Notes:

[6] - Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, time, treatment by time interaction, and stratification factors of HPV status and overall cancer stage

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 88 Months

Adverse event reporting additional description:

All Cause Mortality (ACM): all randomized participants. AEs: all randomized participants who got ≥1 dose of study drug. Per protocol, MedDRA preferred terms "Neoplasm progression (NP), Malignant (NP) and Disease progression" not related to study drug are omitted as AEs

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Pembrolizumab + CRT followed by Pembrolizumab
Reporting group description: -	
Reporting group title	Placebo + CRT followed by Placebo

Reporting group description: -

Serious adverse events	Pembrolizumab + CRT followed by Pembrolizumab	Placebo + CRT followed by Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	245 / 398 (61.56%)	197 / 398 (49.50%)	
number of deaths (all causes)	156	178	
number of deaths resulting from adverse events	35	28	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lip and/or oral cavity cancer			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infected neoplasm			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Follicular thyroid cancer			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Follicular lymphoma			

subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm swelling			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour pain			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour inflammation			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
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	2 / 398 (0.50%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			

subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal squamous cell carcinoma			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-small cell lung cancer			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	2 / 398 (0.50%)	3 / 398 (0.75%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 398 (0.00%)	4 / 398 (1.01%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 398 (0.75%)	8 / 398 (2.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 3	0 / 8	
Face oedema			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrosis			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 398 (1.01%)	3 / 398 (0.75%)	
occurrences causally related to treatment / all	4 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 398 (0.00%)	3 / 398 (0.75%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	10 / 398 (2.51%)	9 / 398 (2.26%)	
occurrences causally related to treatment / all	5 / 10	5 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device occlusion			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent thrombosis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling			

subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 398 (0.50%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	2 / 398 (0.50%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 398 (0.50%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal inflammation			
subjects affected / exposed	3 / 398 (0.75%)	4 / 398 (1.01%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal haemorrhage			
subjects affected / exposed	6 / 398 (1.51%)	3 / 398 (0.75%)	
occurrences causally related to treatment / all	2 / 6	5 / 5	
deaths causally related to treatment / all	0 / 0	3 / 3	

Oropharyngeal pain			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal fistula			
subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	9 / 398 (2.26%)	5 / 398 (1.26%)	
occurrences causally related to treatment / all	3 / 9	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal necrosis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal haemorrhage			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal fistula			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cyst			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottic oedema			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 398 (0.50%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal necrosis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal stenosis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pharyngeal oedema			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal swelling			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal ulceration			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
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 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia lipoid			

subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	10 / 398 (2.51%)	3 / 398 (0.75%)	
occurrences causally related to treatment / all	10 / 11	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 398 (1.01%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	2 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 398 (0.75%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	1 / 398 (0.25%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 398 (0.00%)	3 / 398 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholism			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol abuse			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 398 (0.50%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	3 / 398 (0.75%)	7 / 398 (1.76%)	
occurrences causally related to treatment / all	3 / 3	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	3 / 398 (0.75%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 398 (0.25%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	6 / 398 (1.51%)	5 / 398 (1.26%)	
occurrences causally related to treatment / all	6 / 6	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			

subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
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	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	3 / 398 (0.75%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 398 (0.75%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 398 (0.25%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Alcohol poisoning			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial injury			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrostomy failure			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrostomy tube site complication			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unintentional medical device removal			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy malfunction			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal obstruction			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stoma complication			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation necrosis			
subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation associated pain			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 398 (0.25%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Osteoradionecrosis			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation skin injury			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 398 (0.50%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 398 (0.50%)	3 / 398 (0.75%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral venous sinus thrombosis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 398 (0.50%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	5 / 398 (1.26%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	3 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (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			
Agranulocytosis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	4 / 398 (1.01%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	24 / 398 (6.03%)	7 / 398 (1.76%)	
occurrences causally related to treatment / all	23 / 26	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Hypoacusis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eyelid ptosis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous detachment			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (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 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Achlorhydria			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 398 (0.75%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	3 / 398 (0.75%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Duodenal perforation			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	11 / 398 (2.76%)	12 / 398 (3.02%)	
occurrences causally related to treatment / all	9 / 11	11 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	4 / 398 (1.01%)	4 / 398 (1.01%)	
occurrences causally related to treatment / all	2 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	2 / 398 (0.50%)	5 / 398 (1.26%)	
occurrences causally related to treatment / all	0 / 3	3 / 6	
deaths causally related to treatment / all	0 / 1	1 / 1	
Nausea			

subjects affected / exposed	17 / 398 (4.27%)	7 / 398 (1.76%)	
occurrences causally related to treatment / all	17 / 19	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	5 / 398 (1.26%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	4 / 398 (1.01%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary hypersecretion			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (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	12 / 398 (3.02%)	12 / 398 (3.02%)	
occurrences causally related to treatment / all	11 / 12	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue oedema			
subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	15 / 398 (3.77%)	10 / 398 (2.51%)	
occurrences causally related to treatment / all	14 / 17	9 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	2 / 398 (0.50%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis sclerosing			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis fulminant			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	2 / 398 (0.50%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis acneiform			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pemphigoid			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash macular			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dysuria			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 398 (0.25%)	5 / 398 (1.26%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	33 / 398 (8.29%)	30 / 398 (7.54%)	
occurrences causally related to treatment / all	38 / 41	28 / 33	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trismus			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess jaw			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abscess neck			
subjects affected / exposed	2 / 398 (0.50%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	4 / 398 (1.01%)	3 / 398 (0.75%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site abscess			

subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	6 / 398 (1.51%)	3 / 398 (0.75%)	
occurrences causally related to treatment / all	1 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 398 (0.50%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis infected			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 398 (0.50%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			

subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungaemia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genitourinary tract infection			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B reactivation			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected fistula			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			

subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinitis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral bacterial infection			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchitis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	43 / 398 (10.80%)	25 / 398 (6.28%)	
occurrences causally related to treatment / all	14 / 49	3 / 33	
deaths causally related to treatment / all	1 / 12	0 / 6	
Pneumonia aspiration			
subjects affected / exposed	12 / 398 (3.02%)	5 / 398 (1.26%)	
occurrences causally related to treatment / all	3 / 12	1 / 6	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	12 / 398 (3.02%)	7 / 398 (1.76%)	
occurrences causally related to treatment / all	1 / 12	2 / 7	
deaths causally related to treatment / all	0 / 4	1 / 2	
Septic shock			
subjects affected / exposed	3 / 398 (0.75%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Skin bacterial infection			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site cellulitis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic infection			

subjects affected / exposed	2 / 398 (0.50%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy infection			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (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	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site infection			
subjects affected / exposed	2 / 398 (0.50%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 398 (1.01%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site infection			

subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	2 / 398 (0.50%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 398 (0.50%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 398 (1.01%)	5 / 398 (1.26%)	
occurrences causally related to treatment / all	3 / 4	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	9 / 398 (2.26%)	5 / 398 (1.26%)	
occurrences causally related to treatment / all	7 / 10	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			

subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	6 / 398 (1.51%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	3 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Latent autoimmune diabetes in adults			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	2 / 398 (0.50%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	10 / 398 (2.51%)	3 / 398 (0.75%)	
occurrences causally related to treatment / all	7 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	3 / 398 (0.75%)	3 / 398 (0.75%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			

subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 398 (0.25%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 398 (0.50%)	1 / 398 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 398 (0.25%)	0 / 398 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 398 (0.00%)	2 / 398 (0.50%)	
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: 5 %

Non-serious adverse events	Pembrolizumab + CRT followed by Pembrolizumab	Placebo + CRT followed by Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	398 / 398 (100.00%)	396 / 398 (99.50%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 398 (5.28%)	33 / 398 (8.29%)	
occurrences (all)	26	38	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	74 / 398 (18.59%)	73 / 398 (18.34%)	
occurrences (all)	93	89	

Fatigue			
subjects affected / exposed	126 / 398 (31.66%)	118 / 398 (29.65%)	
occurrences (all)	150	137	
Localised oedema			
subjects affected / exposed	26 / 398 (6.53%)	28 / 398 (7.04%)	
occurrences (all)	29	29	
Oedema peripheral			
subjects affected / exposed	21 / 398 (5.28%)	18 / 398 (4.52%)	
occurrences (all)	26	20	
Pyrexia			
subjects affected / exposed	64 / 398 (16.08%)	43 / 398 (10.80%)	
occurrences (all)	94	55	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	49 / 398 (12.31%)	62 / 398 (15.58%)	
occurrences (all)	52	69	
Cough			
subjects affected / exposed	65 / 398 (16.33%)	64 / 398 (16.08%)	
occurrences (all)	75	71	
Hiccups			
subjects affected / exposed	32 / 398 (8.04%)	25 / 398 (6.28%)	
occurrences (all)	40	32	
Dyspnoea			
subjects affected / exposed	20 / 398 (5.03%)	20 / 398 (5.03%)	
occurrences (all)	24	26	
Productive cough			
subjects affected / exposed	39 / 398 (9.80%)	42 / 398 (10.55%)	
occurrences (all)	45	50	
Pharyngeal inflammation			
subjects affected / exposed	51 / 398 (12.81%)	48 / 398 (12.06%)	
occurrences (all)	52	48	
Oropharyngeal pain			
subjects affected / exposed	91 / 398 (22.86%)	72 / 398 (18.09%)	
occurrences (all)	98	79	
Laryngeal oedema			

subjects affected / exposed	10 / 398 (2.51%)	25 / 398 (6.28%)	
occurrences (all)	10	25	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	57 / 398 (14.32%)	43 / 398 (10.80%)	
occurrences (all)	61	50	
Anxiety			
subjects affected / exposed	22 / 398 (5.53%)	14 / 398 (3.52%)	
occurrences (all)	24	14	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	79 / 398 (19.85%)	60 / 398 (15.08%)	
occurrences (all)	100	74	
Aspartate aminotransferase increased			
subjects affected / exposed	59 / 398 (14.82%)	41 / 398 (10.30%)	
occurrences (all)	78	49	
Blood creatinine increased			
subjects affected / exposed	92 / 398 (23.12%)	87 / 398 (21.86%)	
occurrences (all)	128	129	
Gamma-glutamyltransferase increased			
subjects affected / exposed	47 / 398 (11.81%)	36 / 398 (9.05%)	
occurrences (all)	61	40	
Lymphocyte count decreased			
subjects affected / exposed	95 / 398 (23.87%)	109 / 398 (27.39%)	
occurrences (all)	143	147	
Neutrophil count decreased			
subjects affected / exposed	166 / 398 (41.71%)	152 / 398 (38.19%)	
occurrences (all)	228	240	
Platelet count decreased			
subjects affected / exposed	97 / 398 (24.37%)	83 / 398 (20.85%)	
occurrences (all)	150	120	
Weight decreased			
subjects affected / exposed	179 / 398 (44.97%)	183 / 398 (45.98%)	
occurrences (all)	192	201	
White blood cell count decreased			

subjects affected / exposed	127 / 398 (31.91%)	135 / 398 (33.92%)	
occurrences (all)	224	236	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	254 / 398 (63.82%)	242 / 398 (60.80%)	
occurrences (all)	260	244	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	34 / 398 (8.54%)	39 / 398 (9.80%)	
occurrences (all)	36	42	
Headache			
subjects affected / exposed	39 / 398 (9.80%)	49 / 398 (12.31%)	
occurrences (all)	46	54	
Dysgeusia			
subjects affected / exposed	132 / 398 (33.17%)	134 / 398 (33.67%)	
occurrences (all)	137	139	
Dizziness			
subjects affected / exposed	30 / 398 (7.54%)	24 / 398 (6.03%)	
occurrences (all)	42	28	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	229 / 398 (57.54%)	205 / 398 (51.51%)	
occurrences (all)	298	287	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	80 / 398 (20.10%)	49 / 398 (12.31%)	
occurrences (all)	84	51	
Tinnitus			
subjects affected / exposed	75 / 398 (18.84%)	88 / 398 (22.11%)	
occurrences (all)	83	92	
Ear pain			
subjects affected / exposed	28 / 398 (7.04%)	33 / 398 (8.29%)	
occurrences (all)	29	35	
Gastrointestinal disorders			
Stomatitis			

subjects affected / exposed	249 / 398 (62.56%)	232 / 398 (58.29%)	
occurrences (all)	279	259	
Abdominal pain upper			
subjects affected / exposed	22 / 398 (5.53%)	13 / 398 (3.27%)	
occurrences (all)	23	13	
Constipation			
subjects affected / exposed	179 / 398 (44.97%)	174 / 398 (43.72%)	
occurrences (all)	218	213	
Diarrhoea			
subjects affected / exposed	88 / 398 (22.11%)	82 / 398 (20.60%)	
occurrences (all)	121	106	
Dry mouth			
subjects affected / exposed	191 / 398 (47.99%)	173 / 398 (43.47%)	
occurrences (all)	206	194	
Dyspepsia			
subjects affected / exposed	26 / 398 (6.53%)	25 / 398 (6.28%)	
occurrences (all)	34	26	
Dysphagia			
subjects affected / exposed	177 / 398 (44.47%)	165 / 398 (41.46%)	
occurrences (all)	190	185	
Gastrooesophageal reflux disease			
subjects affected / exposed	30 / 398 (7.54%)	19 / 398 (4.77%)	
occurrences (all)	31	21	
Nausea			
subjects affected / exposed	222 / 398 (55.78%)	232 / 398 (58.29%)	
occurrences (all)	324	337	
Odynophagia			
subjects affected / exposed	87 / 398 (21.86%)	89 / 398 (22.36%)	
occurrences (all)	96	98	
Oral pain			
subjects affected / exposed	28 / 398 (7.04%)	22 / 398 (5.53%)	
occurrences (all)	30	23	
Saliva altered			
subjects affected / exposed	22 / 398 (5.53%)	26 / 398 (6.53%)	
occurrences (all)	23	26	
Vomiting			

subjects affected / exposed	131 / 398 (32.91%)	116 / 398 (29.15%)	
occurrences (all)	204	168	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	59 / 398 (14.82%)	24 / 398 (6.03%)	
occurrences (all)	70	26	
Pruritus			
subjects affected / exposed	52 / 398 (13.07%)	27 / 398 (6.78%)	
occurrences (all)	57	34	
Erythema			
subjects affected / exposed	27 / 398 (6.78%)	19 / 398 (4.77%)	
occurrences (all)	28	21	
Alopecia			
subjects affected / exposed	15 / 398 (3.77%)	22 / 398 (5.53%)	
occurrences (all)	15	23	
Dry skin			
subjects affected / exposed	17 / 398 (4.27%)	21 / 398 (5.28%)	
occurrences (all)	18	21	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	52 / 398 (13.07%)	39 / 398 (9.80%)	
occurrences (all)	74	53	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	40 / 398 (10.05%)	33 / 398 (8.29%)	
occurrences (all)	43	35	
Hypothyroidism			
subjects affected / exposed	100 / 398 (25.13%)	54 / 398 (13.57%)	
occurrences (all)	110	58	
Musculoskeletal and connective tissue disorders			
Trismus			
subjects affected / exposed	12 / 398 (3.02%)	23 / 398 (5.78%)	
occurrences (all)	14	25	
Neck pain			
subjects affected / exposed	35 / 398 (8.79%)	36 / 398 (9.05%)	
occurrences (all)	38	38	

Arthralgia			
subjects affected / exposed	25 / 398 (6.28%)	28 / 398 (7.04%)	
occurrences (all)	34	34	
Back pain			
subjects affected / exposed	21 / 398 (5.28%)	14 / 398 (3.52%)	
occurrences (all)	26	14	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 398 (3.52%)	20 / 398 (5.03%)	
occurrences (all)	15	20	
Oral candidiasis			
subjects affected / exposed	77 / 398 (19.35%)	60 / 398 (15.08%)	
occurrences (all)	85	71	
Pneumonia			
subjects affected / exposed	23 / 398 (5.78%)	21 / 398 (5.28%)	
occurrences (all)	25	23	
Urinary tract infection			
subjects affected / exposed	26 / 398 (6.53%)	17 / 398 (4.27%)	
occurrences (all)	35	21	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	104 / 398 (26.13%)	115 / 398 (28.89%)	
occurrences (all)	115	126	
Dehydration			
subjects affected / exposed	44 / 398 (11.06%)	38 / 398 (9.55%)	
occurrences (all)	49	48	
Hyperglycaemia			
subjects affected / exposed	31 / 398 (7.79%)	35 / 398 (8.79%)	
occurrences (all)	44	51	
Hyperkalaemia			
subjects affected / exposed	27 / 398 (6.78%)	36 / 398 (9.05%)	
occurrences (all)	38	52	
Hyperuricaemia			
subjects affected / exposed	31 / 398 (7.79%)	33 / 398 (8.29%)	
occurrences (all)	41	50	
Hypoalbuminaemia			

subjects affected / exposed	41 / 398 (10.30%)	33 / 398 (8.29%)	
occurrences (all)	51	41	
Hypocalcaemia			
subjects affected / exposed	38 / 398 (9.55%)	31 / 398 (7.79%)	
occurrences (all)	48	42	
Hypokalaemia			
subjects affected / exposed	100 / 398 (25.13%)	74 / 398 (18.59%)	
occurrences (all)	142	108	
Hypomagnesaemia			
subjects affected / exposed	110 / 398 (27.64%)	96 / 398 (24.12%)	
occurrences (all)	163	144	
Hyponatraemia			
subjects affected / exposed	79 / 398 (19.85%)	71 / 398 (17.84%)	
occurrences (all)	109	109	
Hypophosphataemia			
subjects affected / exposed	30 / 398 (7.54%)	19 / 398 (4.77%)	
occurrences (all)	33	32	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 May 2017	AM2: Revision of retropharyngeal (RT) dose parameters to ensure standardization and uniformity of treatment for study while providing flexibility for global radiation therapy practices.
26 April 2018	AM4: Updated guidelines for dose modification to align with the most current label and safety information for pembrolizumab.
30 September 2019	AM6: 1) To align the protocol-specified criteria for locoregional failure with the definition of an event considering that protocol- specified locoregional failures are also clinically significant events. 2) Events in patients with locally advanced head and neck squamous cell carcinoma (SCC) treated with definitive chemoradiation therapy (CRT) can occur in the absence of radiographic progression per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) by Blinded Independent Central Review (BICR). Therefore, the Event Free Survival (EFS) definition is being revised accordingly to clarify the scenarios in which histological confirmation of invasive cancer secondary to residual and/or progressive disease fulfills criteria for an event in the absence of radiographic progression per RECIST 1.1 by BICR.
16 December 2020	AM7: 1) To update the assumptions of the survival distribution of the control arm based on emerging data from JAVELIN 100; and to update the timing of efficacy analysis to allow for additional follow-up of all subjects. 2) To allow imaging assessments to continue for subjects who have not experienced an event. Censoring rules have been changed accordingly. 3) Collection of Fludeoxyglucose Positron Emission Tomography (FDG-PET) reports and corresponding imaging (Computed Tomography (CT)/Magnetic Resonance Imaging (MRI)) reports to fulfill a regulatory request.
21 November 2022	AM8: Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. Additionally, scheduled trial assessments/procedures were modified based on the results of the final efficacy analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported