Clinical trial results:
A Randomized Phase 3 Study of Nivolumab Plus Ipilimumab or Nivolumab Combined With Fluorouracil Plus Cisplatin Versus Fluorouracil Plus Cisplatin in Subjects With Unresectable Advanced, Recurrent or Metastatic Previously Untreated Esophageal Squamous Cell Carcinoma

Summary

EudraCT number	2016-001514-20
Trial protocol	CZ ES GB PL FR DK PT IT RO
Global end of trial date	13 January 2025

Results information

Result version number	v1 (current)
This version publication date	23 January 2026
First version publication date	23 January 2026

Trial information

Trial identification

Sponsor protocol code	CA209-648

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03143153
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium,
Public contact	Global Submission Management, Clinical Trials, Bristol-Myers Squibb International Corporation, mg-gsm-ct@bms.com
Scientific contact	Global Submission Management, Clinical Trials, Bristol-Myers Squibb International Corporation, Clinical.Trails@bms.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	16 February 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 January 2021
Global end of trial reached?	Yes
Global end of trial date	13 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to compare how long subjects with esophageal cancer live overall or live without disease progression after receiving nivolumab and ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 18
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Brazil: 50
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Chile: 7
Country: Number of subjects enrolled	China: 112
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Hong Kong: 9
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Japan: 395
Country: Number of subjects enrolled	Korea, Republic of: 63
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Peru: 7

Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Romania: 26
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Taiwan: 94
Country: Number of subjects enrolled	Türkiye: 6
Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	970
EEA total number of subjects	112

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)	518
From 65 to 84 years	449
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

970 participants randomized, 936 treated.

Period 1

Period 1 title	Pre-Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Nivolumab + Ipilimumab

Arm description:

Participants will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks.

Arm type	Experimental
Investigational medicinal product name	No Treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

No Treatment

Arm title	Arm B: Nivolumab + Chemotherapy

Arm description:

Participants will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Arm C: Chemotherapy

Arm description:

Participants will receive treatment with fluorouracil 800 mg/m²/day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Arm A: Nivolumab + Ipilimumab	Arm B: Nivolumab + Chemotherapy	Arm C: Chemotherapy
Started	325	321	324
Completed	322	310	304
Not completed	3	11	20
Participant withdrew consent	-	1	12
Other Reasons	1	2	1
Participant no longer meets study criteria	-	4	2
Adverse event unrelated to study drug	1	3	1
Disease Progression	1	1	2
Participant request to discontinue study treatment	-	-	2

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Nivolumab + Ipilimumab

Arm description:

Participants will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

30 minutes infusion 1mg/kg

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg as 30 minutes infusion

Arm title	Arm B: Nivolumab + Chemotherapy

Arm description:

Participants will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.

Arm type	Experimental

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

240 mg as 30 minutes infusion

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m² as a 30- to 120-minute infusion

Investigational medicinal product name	Flurouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

800 mg/m²/day as an IV continuous infusion

Arm title	Arm C: Chemotherapy

Arm description:

Participants will receive treatment with fluorouracil 800 mg/m²/day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.

Arm type	Active comparator
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m² as a 30- to 120-minute infusion

Investigational medicinal product name	Flurouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

800 mg/m²/day as an IV continuous infusion

Number of subjects in period 2	Arm A: Nivolumab + Ipilimumab	Arm B: Nivolumab + Chemotherapy	Arm C: Chemotherapy
Started	322	310	304
Completed	28	14	0
Not completed	294	296	304
Adverse event, serious fatal	6	4	4

Participant withdrew consent	3	4	12
Study drug toxicity	59	36	38
Other Reasons	10	10	15
Maximum clinical benefit	1	3	4
Pregnancy	1	-	-
Adverse event unrelated to study drug	19	26	11
Disease Progression	182	191	199
Participant request to discontinue study treatment	13	22	21

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Nivolumab + Ipilimumab
Reporting group description:	
Participants will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks.	
Reporting group title	Arm B: Nivolumab + Chemotherapy
Reporting group description:	
Participants will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.	
Reporting group title	Arm C: Chemotherapy
Reporting group description:	
Participants will receive treatment with fluorouracil 800 mg/m²/day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.	

Reporting group values	Arm A: Nivolumab + Ipilimumab	Arm B: Nivolumab + Chemotherapy	Arm C: Chemotherapy
Number of subjects	325	321	324
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	185	167	166
From 65-84 years	140	151	158
85 years and over	0	3	0
Age Continuous Units: Years			
arithmetic mean	62.2	63.1	63.3
standard deviation	± 9.1	± 9.2	± 8.7
Sex: Female, Male Units: Participants			
Female	56	68	49
Male	269	253	275
Race/Ethnicity, Customized Units: Subjects			
White	79	85	84
Black or African American	4	1	6
American Indian or Alaska Native	1	2	1
Asian Indian	1	4	3
Chinese	71	74	70
Japanese	131	126	137
Asian Other	28	23	17
Other	10	6	6

Reporting group values	Total		
Number of subjects	970		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	518		
From 65-84 years	449		
85 years and over	3		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	173		
Male	797		
Race/Ethnicity, Customized Units: Subjects			
White	248		
Black or African American	11		
American Indian or Alaska Native	4		
Asian Indian	8		
Chinese	215		
Japanese	394		
Asian Other	68		
Other	22		

End points

End points reporting groups

Reporting group title	Arm A: Nivolumab + Ipilimumab
Reporting group description:	
Participants will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks.	
Reporting group title	Arm B: Nivolumab + Chemotherapy
Reporting group description:	
Participants will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.	
Reporting group title	Arm C: Chemotherapy
Reporting group description:	
Participants will receive treatment with fluorouracil 800 mg/m²/day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.	
Reporting group title	Arm A: Nivolumab + Ipilimumab
Reporting group description:	
Participants will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks.	
Reporting group title	Arm B: Nivolumab + Chemotherapy
Reporting group description:	
Participants will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.	
Reporting group title	Arm C: Chemotherapy
Reporting group description:	
Participants will receive treatment with fluorouracil 800 mg/m²/day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.	

Primary: Overall Survival (OS) in participants with tumor cell PD-L1

End point title	Overall Survival (OS) in participants with tumor cell PD-L1
End point description:	
Overall Survival (OS) is defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS will be censored on the last date the subject was known to be alive.	
End point type	Primary
End point timeframe:	
From the date of randomization to up to the date of death (up to approximately 20 months)	

End point values	Arm A: Nivolumab + Ipilimumab	Arm B: Nivolumab + Chemotherapy	Arm C: Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	158	157	
Units: Months				
median (confidence interval 95%)	13.70 (11.24 to 17.02)	15.44 (11.93 to 19.52)	9.07 (7.69 to 9.95)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Hazard Ratio is Arm A: Nivolumab + Ipilimumab over Arm C: Chemotherapy.	
Comparison groups	Arm A: Nivolumab + Ipilimumab v Arm C: Chemotherapy
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	Other: 98.6 %
sides	2-sided
lower limit	0.46
upper limit	0.9

Notes:

[1] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Hazard Ratio is Arm A: Nivolumab + Ipilimumab over Arm C: Chemotherapy.	
Comparison groups	Arm A: Nivolumab + Ipilimumab v Arm C: Chemotherapy
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.84

Notes:

[2] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Hazard Ratio is Arm B: Nivolumab + Chemotherapy over Arm C: Chemotherapy	
Comparison groups	Arm B: Nivolumab + Chemotherapy v Arm C: Chemotherapy

Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	Other: 99.5 %
sides	2-sided
lower limit	0.37
upper limit	0.8

Notes:

[3] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Hazard Ratio is Arm B: Nivolumab + Chemotherapy over Arm C: Chemotherapy

Comparison groups	Arm B: Nivolumab + Chemotherapy v Arm C: Chemotherapy
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.71

Notes:

[4] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT.

Primary: Progression-free survival (PFS) as assessed by BICR in participants with tumor cell PD-L1

End point title	Progression-free survival (PFS) as assessed by BICR in participants with tumor cell PD-L1

End point description:

Progression-free survival (PFS) is defined as the time from randomization to the date of the first documented progressive disease (PD) per Blinded Independent Central Review (BICR) or death due to any cause. Participants who die without a reported prior PD per BICR (and die without start of subsequent therapy) will be considered to have progressed on the date of death. Participants who did not have documented PD per BICR per RECIST1.1 criteria and who did not die, will be censored at the date of the last evaluable tumor assessment on or prior to initiation of the subsequent anti-cancer therapy. Participants who did not have any on-study tumor assessments and did not die (or died after initiation of the subsequent anti-cancer therapy) will be censored at the randomization date. Participants who started any subsequent anti-cancer therapy without a prior reported PD per BICR will be censored at the last tumor assessment on or prior to initiation of the subsequent anti-cancer therapy.

End point type	Primary

End point timeframe:

From the date of randomization to up to the date of the first documented disease progression or death (up to approximately 9 months)

End point values	Arm A: Nivolumab + Ipilimumab	Arm B: Nivolumab + Chemotherapy	Arm C: Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	158	157	
Units: Months				
median (confidence interval 95%)	4.04 (2.40 to 4.93)	6.93 (5.68 to 8.34)	4.44 (2.89 to 5.82)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Hazard Ratio is Arm A: Nivolumab + Ipilimumab over Arm C: Chemotherapy	
Comparison groups	Arm A: Nivolumab + Ipilimumab v Arm C: Chemotherapy
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8958 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	Other: 98.5 %
sides	2-sided
lower limit	0.73
upper limit	1.43

Notes:

[5] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Hazard Ratio is Arm B: Nivolumab + Chemotherapy over Arm C: Chemotherapy	
Comparison groups	Arm B: Nivolumab + Chemotherapy v Arm C: Chemotherapy
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0023 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.86

Notes:

[6] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Hazard Ratio is Arm B: Nivolumab + Chemotherapy over Arm C: Chemotherapy

Comparison groups	Arm B: Nivolumab + Chemotherapy v Arm C: Chemotherapy
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0023 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	Other: 98.5 %
sides	2-sided
lower limit	0.46
upper limit	0.92

Notes:

[7] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Hazard Ratio is Arm A: Nivolumab + Ipilimumab over Arm C: Chemotherapy

Comparison groups	Arm A: Nivolumab + Ipilimumab v Arm C: Chemotherapy
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8958 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.34

Notes:

[8] - Log-rank test stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT

Secondary: Overall Survival (OS) in all randomized participants

End point title	Overall Survival (OS) in all randomized participants

End point description:

Overall Survival (OS) is defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS will be censored on the last date the subject was known to be alive.

End point type	Secondary

End point timeframe:

From the date of randomization to up to the date of death (up to approximately 88 months)

End point values	Arm A: Nivolumab + Ipilimumab	Arm B: Nivolumab + Chemotherapy	Arm C: Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	325	321	324	
Units: Months				
median (confidence interval 95%)	12.747 (11.269 to 15.474)	13.207 (11.105 to 15.671)	10.710 (9.396 to 12.090)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Hazard Ratio is Arm B: Nivolumab + Chemotherapy over Arm C: Chemotherapy	
Comparison groups	Arm B: Nivolumab + Chemotherapy v Arm C: Chemotherapy
Number of subjects included in analysis	645
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.92

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Hazard Ratio is Arm A: Nivolumab + Ipilimumab over Arm C: Chemotherapy	
Comparison groups	Arm A: Nivolumab + Ipilimumab v Arm C: Chemotherapy
Number of subjects included in analysis	649
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.92

Secondary: Progression-free survival (PFS) in all randomized participants as assessed by BICR

End point title	Progression-free survival (PFS) in all randomized participants as assessed by BICR

End point description:

Progression-free survival (PFS) is defined as the time from randomization to the date of the first documented progressive disease (PD) per Blinded Independent Central Review (BICR) or death due to any cause. Participants who die without a reported prior PD per BICR (and die without start of subsequent therapy) will be considered to have progressed on the date of death. Participants who did not have documented PD per BICR per RECIST1.1 criteria and who did not die, will be censored at the date of the last evaluable tumor assessment on or prior to initiation of the subsequent anti-cancer therapy. Participants who did not have any on-study tumor assessments and did not die (or died after initiation of the subsequent anti-cancer therapy) will be censored at the randomization date. Participants who started any subsequent anti-cancer therapy without a prior reported PD per BICR will be censored at the last tumor assessment on or prior to initiation of the subsequent anti-cancer therapy.

End point type	Secondary

End point timeframe:

From the date of randomization to up to the date of the first documented disease progression or death (up to approximately 88 months)

End point values	Arm A: Nivolumab + Ipilimumab	Arm B: Nivolumab + Chemotherapy	Arm C: Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	325	321	324	
Units: Months				
median (confidence interval 95%)	2.891 (2.661 to 4.172)	5.782 (5.520 to 6.998)	5.618 (4.304 to 5.914)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Hazard Ratio is Arm B: Nivolumab + Chemotherapy over Arm C: Chemotherapy

Comparison groups	Arm B: Nivolumab + Chemotherapy v Arm C: Chemotherapy
Number of subjects included in analysis	645
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:	
Hazard Ratio is Arm A: Nivolumab + Ipilimumab over Arm C: Chemotherapy	
Comparison groups	Arm A: Nivolumab + Ipilimumab v Arm C: Chemotherapy
Number of subjects included in analysis	649
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.5

Secondary: Objective Response Rate (ORR) as assessed by BICR

End point title	Objective Response Rate (ORR) as assessed by BICR

End point description:

Objective response rate (ORR) is defined as the percentage of participants with a best overall response (BOR) of complete response (CR) or partial response (PR). Best overall response (BOR) is defined as the best response designation as determined by BICR, recorded between the date of randomization and the date of objectively documented progression (per RECIST 1.1) or the date of subsequent anti-cancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. Partial response is defined as at least a 30% decrease in the sum of diameters of target lesions. Complete response is defined as the disappearance of all target lesions and the reduction of any pathological lymph nodes to <10 mm.

End point type	Secondary

End point timeframe:

From the date of randomization to up to the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first (up to 88 months)

End point values	Arm A: Nivolumab + Ipilimumab	Arm B: Nivolumab + Chemotherapy	Arm C: Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	325	321	324	
Units: Percentage of participants				
number (confidence interval 95%)				
Participants with baseline PD-L1 status < 1%	20.1 (14.3 to 27.1)	41.7 (34.1 to 49.7)	33.7 (26.6 to 41.5)	
Participants with baseline PD-L1 status >= 1%	35.4 (28.0 to 43.4)	53.2 (45.1 to 61.1)	19.9 (13.9 to 27.0)	
Participants with baseline PD-L1 status < 5%	22.3 (16.7 to 28.6)	44.8 (37.8 to 51.9)	30.9 (24.7 to 37.7)	
Participants with baseline PD-L1 status >= 5%	36.7 (28.1 to 45.9)	51.7 (42.4 to 60.9)	20.0 (13.1 to 28.5)	
Participants with baseline PD-L1 status < 10%	23.3 (17.9 to 29.5)	46.1 (39.4 to 53.0)	29.3 (23.5 to 35.8)	
Participants with baseline PD-L1 status >= 10%	36.9 (27.6 to 47.0)	50.0 (39.9 to 60.1)	21.6 (13.9 to 31.2)	
Participants with baseline PD-L1 missing	33.3 (0.8 to 90.6)	99999 (99999 to 99999)	0.0 (0.0 to 84.2)	

All randomized participants	27.4 (22.6 to 32.6)	47.4 (41.8 to 53.0)	26.9 (22.1 to 32.0)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All cause mortality was collected till 88 months and Serious and Non-Serious AEs from first dose (Day 1) to 100 days post last dose (up to 43 months)

Adverse event reporting additional description:

All cause mortality was collected for all the randomized participants and serious and non-serious adverse events were collected for treated population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Arm A: Nivolumab + Ipilimumab

Reporting group description:

Participants will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab as a 30-minute infusion 1 mg/kg every 6 weeks.

Reporting group title	Arm C: Chemotherapy

Reporting group description:

Participants will receive treatment with fluorouracil 800 mg/m²/day as an IV continuous infusion from Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.

Reporting group title	Arm B: Nivolumab + Chemotherapy

Reporting group description:

Participants will receive treatment with nivolumab 240 mg as a 30-minute infusion on Day 1 and Day 15, fluorouracil 800 mg/m²/day as an IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of 4-week cycle.

Serious adverse events	Arm A: Nivolumab + Ipilimumab	Arm C: Chemotherapy	Arm B: Nivolumab + Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	243 / 322 (75.47%)	174 / 304 (57.24%)	226 / 310 (72.90%)
number of deaths (all causes)	267	266	262
number of deaths resulting from adverse events	85	75	82
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adult T-cell lymphoma/leukaemia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign neoplasm			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cancer pain			
subjects affected / exposed	3 / 322 (0.93%)	1 / 304 (0.33%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	59 / 322 (18.32%)	65 / 304 (21.38%)	61 / 310 (19.68%)
occurrences causally related to treatment / all	0 / 59	0 / 66	0 / 63
deaths causally related to treatment / all	0 / 49	0 / 58	0 / 49
Lipoma			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal cancer			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopharyngeal cancer			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal adenoma			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone marrow			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tumour compression			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to kidney			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour fistulisation			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 322 (0.00%)	3 / 304 (0.99%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tumour pain			
subjects affected / exposed	1 / 322 (0.31%)	4 / 304 (1.32%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Deep vein thrombosis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Poor venous access			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 322 (0.62%)	3 / 304 (0.99%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Internal haemorrhage			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	0 / 322 (0.00%)	2 / 304 (0.66%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Oesophageal operation			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Assisted suicide			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 322 (1.55%)	1 / 304 (0.33%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site discharge			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication associated with device			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	5 / 322 (1.55%)	0 / 304 (0.00%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 5	0 / 0	0 / 2
Mucosal inflammation			
subjects affected / exposed	0 / 322 (0.00%)	2 / 304 (0.66%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 0	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	2 / 322 (0.62%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 1
Feeling cold			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	3 / 322 (0.93%)	1 / 304 (0.33%)	3 / 310 (0.97%)
occurrences causally related to treatment / all	1 / 3	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nodule			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	14 / 322 (4.35%)	7 / 304 (2.30%)	7 / 310 (2.26%)
occurrences causally related to treatment / all	6 / 17	1 / 7	2 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 322 (0.31%)	2 / 304 (0.66%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 2
Polyp			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic shock			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1

Acute respiratory distress syndrome			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchostenosis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial obstruction			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	5 / 322 (1.55%)	2 / 304 (0.66%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	1 / 6	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hiccups			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 322 (0.00%)	2 / 304 (0.66%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinal disorder			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	5 / 322 (1.55%)	2 / 304 (0.66%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	6 / 6	0 / 2	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Immune-mediated lung disease			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagobronchial fistula			

subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	4 / 322 (1.24%)	1 / 304 (0.33%)	5 / 310 (1.61%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	4 / 310 (1.29%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 3
Pulmonary thrombosis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 322 (0.62%)	3 / 304 (0.99%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	1 / 2	3 / 3	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	13 / 322 (4.04%)	1 / 304 (0.33%)	6 / 310 (1.94%)
occurrences causally related to treatment / all	13 / 13	0 / 1	9 / 9
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Stridor			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal stenosis			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal fistula			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Depression			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Logorrhoea			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device breakage			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patient-device incompatibility			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 322 (0.93%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adjusted calcium increased			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anticoagulation drug level above therapeutic			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood sodium decreased			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			

subjects affected / exposed	3 / 322 (0.93%)	1 / 304 (0.33%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	2 / 3	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood calcium increased			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	4 / 310 (1.29%)
occurrences causally related to treatment / all	0 / 1	0 / 1	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram Q wave abnormal			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cortisol decreased			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 322 (0.00%)	2 / 304 (0.66%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 0	2 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urine output decreased			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrio-oesophageal fistula			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Brain contusion			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heat illness			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			

subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Stoma site discharge			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation oesophagitis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	5 / 322 (1.55%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site pain			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal obstruction			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	1 / 322 (0.31%)	2 / 304 (0.66%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure congestive			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Atrial fibrillation			
subjects affected / exposed	1 / 322 (0.31%)	3 / 304 (0.99%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	7 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriospasm coronary			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Palpitations			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	2 / 322 (0.62%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem haemorrhage			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated encephalopathy			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated encephalitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stupor			

subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural hygroma			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 322 (1.86%)	7 / 304 (2.30%)	5 / 310 (1.61%)
occurrences causally related to treatment / all	0 / 6	2 / 8	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	6 / 322 (1.86%)	5 / 304 (1.64%)	7 / 310 (2.26%)
occurrences causally related to treatment / all	0 / 6	3 / 5	4 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenia			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelosuppression			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic haematoma			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye pain			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vogt-Koyanagi-Harada disease			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			

subjects affected / exposed	1 / 322 (0.31%)	2 / 304 (0.66%)	3 / 310 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 322 (0.31%)	2 / 304 (0.66%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	5 / 322 (1.55%)	3 / 304 (0.99%)	7 / 310 (2.26%)
occurrences causally related to treatment / all	2 / 5	3 / 3	4 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diaphragmatic hernia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 322 (0.62%)	1 / 304 (0.33%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	4 / 322 (1.24%)	0 / 304 (0.00%)	5 / 310 (1.61%)
occurrences causally related to treatment / all	4 / 4	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aorto-oesophageal fistula			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric fistula			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	12 / 322 (3.73%)	16 / 304 (5.26%)	21 / 310 (6.77%)
occurrences causally related to treatment / all	0 / 13	0 / 20	1 / 28
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	5 / 322 (1.55%)	2 / 304 (0.66%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 5	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haematemesis			
subjects affected / exposed	2 / 322 (0.62%)	2 / 304 (0.66%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated enterocolitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 322 (0.00%)	2 / 304 (0.66%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant ascites			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nausea			
subjects affected / exposed	2 / 322 (0.62%)	5 / 304 (1.64%)	4 / 310 (1.29%)
occurrences causally related to treatment / all	1 / 2	3 / 5	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Odynophagia			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal mass			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal haemorrhage			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Oesophageal fistula			
subjects affected / exposed	0 / 322 (0.00%)	3 / 304 (0.99%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal motility disorder			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal obstruction			
subjects affected / exposed	3 / 322 (0.93%)	5 / 304 (1.64%)	3 / 310 (0.97%)
occurrences causally related to treatment / all	2 / 4	0 / 5	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	4 / 322 (1.24%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagomediastinal fistula			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal-pulmonary fistula			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	3 / 322 (0.93%)	13 / 304 (4.28%)	9 / 310 (2.90%)
occurrences causally related to treatment / all	0 / 3	1 / 13	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal perforation			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	3 / 310 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Oesophageal pain			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumatosis intestinalis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Rectal perforation			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	6 / 310 (1.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	4 / 322 (1.24%)	2 / 304 (0.66%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Vomiting			
subjects affected / exposed	5 / 322 (1.55%)	12 / 304 (3.95%)	4 / 310 (1.29%)
occurrences causally related to treatment / all	4 / 6	9 / 12	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary obstruction			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	3 / 322 (0.93%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			

subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatic function abnormal			
subjects affected / exposed	9 / 322 (2.80%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	8 / 9	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema multiforme			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	3 / 322 (0.93%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous emphysema			

subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	2 / 322 (0.62%)	4 / 304 (1.32%)	9 / 310 (2.90%)
occurrences causally related to treatment / all	1 / 2	3 / 4	6 / 9
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 2
Hydronephrosis			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 322 (0.00%)	2 / 304 (0.66%)	3 / 310 (0.97%)
occurrences causally related to treatment / all	0 / 0	2 / 2	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenocorticotropic hormone deficiency			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	8 / 322 (2.48%)	0 / 304 (0.00%)	3 / 310 (0.97%)
occurrences causally related to treatment / all	7 / 8	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypercalcaemia of malignancy			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorder			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	6 / 322 (1.86%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed	7 / 322 (2.17%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	6 / 7	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	3 / 322 (0.93%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Secondary adrenocortical insufficiency			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroiditis			

subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated arthritis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gouty arthritis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteolysis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	2 / 322 (0.62%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 322 (0.00%)	3 / 304 (0.99%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			

subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bacterial infection			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis bacterial			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis bacterial			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine infection			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph gland infection			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 322 (0.62%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinitis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral infection			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis viral			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 322 (0.00%)	3 / 304 (0.99%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Parotitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	32 / 322 (9.94%)	20 / 304 (6.58%)	33 / 310 (10.65%)
occurrences causally related to treatment / all	0 / 35	2 / 23	6 / 40
deaths causally related to treatment / all	0 / 6	1 / 3	1 / 6
Pneumonia aspiration			
subjects affected / exposed	12 / 322 (3.73%)	8 / 304 (2.63%)	6 / 310 (1.94%)
occurrences causally related to treatment / all	0 / 14	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumonia bacterial			

subjects affected / exposed	4 / 322 (1.24%)	2 / 304 (0.66%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	3 / 310 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
Sepsis			
subjects affected / exposed	4 / 322 (1.24%)	3 / 304 (0.99%)	3 / 310 (0.97%)
occurrences causally related to treatment / all	0 / 4	1 / 3	0 / 3
deaths causally related to treatment / all	0 / 2	1 / 1	0 / 0
Septic shock			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Stoma site cellulitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site infection			

subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethritis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	3 / 310 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	1 / 322 (0.31%)	2 / 304 (0.66%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Decreased appetite			
subjects affected / exposed	9 / 322 (2.80%)	7 / 304 (2.30%)	4 / 310 (1.29%)
occurrences causally related to treatment / all	2 / 9	2 / 7	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	9 / 322 (2.80%)	6 / 304 (1.97%)	4 / 310 (1.29%)
occurrences causally related to treatment / all	3 / 10	4 / 6	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fulminant type 1 diabetes mellitus			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed	5 / 322 (1.55%)	4 / 304 (1.32%)	4 / 310 (1.29%)
occurrences causally related to treatment / all	1 / 5	0 / 4	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	4 / 322 (1.24%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	2 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 322 (0.00%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophagia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 304 (0.33%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	6 / 322 (1.86%)	4 / 304 (1.32%)	4 / 310 (1.29%)
occurrences causally related to treatment / all	6 / 7	4 / 5	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 322 (0.31%)	2 / 304 (0.66%)	4 / 310 (1.29%)
occurrences causally related to treatment / all	1 / 1	1 / 3	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			

subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypernatraemia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 304 (0.00%)	0 / 310 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	2 / 322 (0.62%)	0 / 304 (0.00%)	2 / 310 (0.65%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 322 (0.31%)	1 / 304 (0.33%)	1 / 310 (0.32%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A: Nivolumab + Ipilimumab	Arm C: Chemotherapy	Arm B: Nivolumab + Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	301 / 322 (93.48%)	288 / 304 (94.74%)	307 / 310 (99.03%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	18 / 322 (5.59%)	19 / 304 (6.25%)	15 / 310 (4.84%)
occurrences (all)	19	19	18
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 322 (2.80%)	22 / 304 (7.24%)	24 / 310 (7.74%)
occurrences (all)	15	25	37
Hypotension			

subjects affected / exposed	11 / 322 (3.42%)	16 / 304 (5.26%)	13 / 310 (4.19%)
occurrences (all)	11	19	15
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	56 / 322 (17.39%)	63 / 304 (20.72%)	83 / 310 (26.77%)
occurrences (all)	69	98	121
Asthenia			
subjects affected / exposed	25 / 322 (7.76%)	26 / 304 (8.55%)	24 / 310 (7.74%)
occurrences (all)	29	38	52
Infusion site extravasation			
subjects affected / exposed	6 / 322 (1.86%)	20 / 304 (6.58%)	15 / 310 (4.84%)
occurrences (all)	6	28	24
Malaise			
subjects affected / exposed	27 / 322 (8.39%)	55 / 304 (18.09%)	59 / 310 (19.03%)
occurrences (all)	36	85	108
Pyrexia			
subjects affected / exposed	76 / 322 (23.60%)	48 / 304 (15.79%)	65 / 310 (20.97%)
occurrences (all)	131	59	84
Oedema peripheral			
subjects affected / exposed	32 / 322 (9.94%)	25 / 304 (8.22%)	45 / 310 (14.52%)
occurrences (all)	37	52	67
Mucosal inflammation			
subjects affected / exposed	4 / 322 (1.24%)	30 / 304 (9.87%)	37 / 310 (11.94%)
occurrences (all)	4	41	70
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	14 / 322 (4.35%)	16 / 304 (5.26%)	14 / 310 (4.52%)
occurrences (all)	15	18	17
Pneumonitis			
subjects affected / exposed	17 / 322 (5.28%)	6 / 304 (1.97%)	20 / 310 (6.45%)
occurrences (all)	17	6	21
Hiccups			
subjects affected / exposed	12 / 322 (3.73%)	63 / 304 (20.72%)	53 / 310 (17.10%)
occurrences (all)	15	124	115
Dyspnoea			

subjects affected / exposed	24 / 322 (7.45%)	11 / 304 (3.62%)	14 / 310 (4.52%)
occurrences (all)	27	11	20
Cough			
subjects affected / exposed	40 / 322 (12.42%)	37 / 304 (12.17%)	44 / 310 (14.19%)
occurrences (all)	52	42	51
Psychiatric disorders			
Insomnia			
subjects affected / exposed	33 / 322 (10.25%)	40 / 304 (13.16%)	54 / 310 (17.42%)
occurrences (all)	37	48	63
Investigations			
Neutrophil count decreased			
subjects affected / exposed	12 / 322 (3.73%)	61 / 304 (20.07%)	75 / 310 (24.19%)
occurrences (all)	20	131	188
Lymphocyte count decreased			
subjects affected / exposed	8 / 322 (2.48%)	9 / 304 (2.96%)	16 / 310 (5.16%)
occurrences (all)	14	13	39
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 322 (0.00%)	9 / 304 (2.96%)	20 / 310 (6.45%)
occurrences (all)	0	11	24
Blood creatinine increased			
subjects affected / exposed	13 / 322 (4.04%)	40 / 304 (13.16%)	41 / 310 (13.23%)
occurrences (all)	17	60	71
Blood alkaline phosphatase increased			
subjects affected / exposed	19 / 322 (5.90%)	10 / 304 (3.29%)	22 / 310 (7.10%)
occurrences (all)	23	11	24
Aspartate aminotransferase increased			
subjects affected / exposed	48 / 322 (14.91%)	12 / 304 (3.95%)	28 / 310 (9.03%)
occurrences (all)	61	17	32
Platelet count decreased			
subjects affected / exposed	13 / 322 (4.04%)	36 / 304 (11.84%)	46 / 310 (14.84%)
occurrences (all)	18	73	95
Alanine aminotransferase increased			
subjects affected / exposed	44 / 322 (13.66%)	13 / 304 (4.28%)	26 / 310 (8.39%)
occurrences (all)	60	18	35
Weight decreased			

subjects affected / exposed	43 / 322 (13.35%)	35 / 304 (11.51%)	41 / 310 (13.23%)
occurrences (all)	51	44	51
Weight increased			
subjects affected / exposed	6 / 322 (1.86%)	14 / 304 (4.61%)	25 / 310 (8.06%)
occurrences (all)	8	25	41
White blood cell count decreased			
subjects affected / exposed	12 / 322 (3.73%)	41 / 304 (13.49%)	58 / 310 (18.71%)
occurrences (all)	30	70	141
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 322 (8.07%)	16 / 304 (5.26%)	27 / 310 (8.71%)
occurrences (all)	29	17	33
Dizziness			
subjects affected / exposed	17 / 322 (5.28%)	29 / 304 (9.54%)	18 / 310 (5.81%)
occurrences (all)	19	38	31
Dysgeusia			
subjects affected / exposed	10 / 322 (3.11%)	19 / 304 (6.25%)	23 / 310 (7.42%)
occurrences (all)	10	25	30
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 322 (1.55%)	28 / 304 (9.21%)	31 / 310 (10.00%)
occurrences (all)	7	29	32
Neuropathy peripheral			
subjects affected / exposed	2 / 322 (0.62%)	15 / 304 (4.93%)	22 / 310 (7.10%)
occurrences (all)	2	16	26
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	6 / 322 (1.86%)	23 / 304 (7.57%)	38 / 310 (12.26%)
occurrences (all)	12	38	70
Anaemia			
subjects affected / exposed	84 / 322 (26.09%)	108 / 304 (35.53%)	156 / 310 (50.32%)
occurrences (all)	122	168	265
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	16 / 322 (4.97%)	13 / 304 (4.28%)	22 / 310 (7.10%)
occurrences (all)	17	16	25
Abdominal pain			

subjects affected / exposed	22 / 322 (6.83%)	18 / 304 (5.92%)	23 / 310 (7.42%)
occurrences (all)	24	22	29
Constipation			
subjects affected / exposed	87 / 322 (27.02%)	138 / 304 (45.39%)	142 / 310 (45.81%)
occurrences (all)	104	203	216
Diarrhoea			
subjects affected / exposed	84 / 322 (26.09%)	63 / 304 (20.72%)	98 / 310 (31.61%)
occurrences (all)	114	116	171
Vomiting			
subjects affected / exposed	53 / 322 (16.46%)	60 / 304 (19.74%)	77 / 310 (24.84%)
occurrences (all)	68	95	132
Stomatitis			
subjects affected / exposed	34 / 322 (10.56%)	75 / 304 (24.67%)	100 / 310 (32.26%)
occurrences (all)	43	148	197
Nausea			
subjects affected / exposed	88 / 322 (27.33%)	172 / 304 (56.58%)	207 / 310 (66.77%)
occurrences (all)	119	378	452
Dysphagia			
subjects affected / exposed	39 / 322 (12.11%)	31 / 304 (10.20%)	42 / 310 (13.55%)
occurrences (all)	44	37	52
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	17 / 322 (5.28%)	1 / 304 (0.33%)	3 / 310 (0.97%)
occurrences (all)	22	1	3
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 322 (3.11%)	42 / 304 (13.82%)	42 / 310 (13.55%)
occurrences (all)	10	42	42
Dry skin			
subjects affected / exposed	18 / 322 (5.59%)	12 / 304 (3.95%)	13 / 310 (4.19%)
occurrences (all)	19	12	13
Pruritus			
subjects affected / exposed	59 / 322 (18.32%)	20 / 304 (6.58%)	38 / 310 (12.26%)
occurrences (all)	71	21	52
Rash			

subjects affected / exposed	75 / 322 (23.29%)	22 / 304 (7.24%)	43 / 310 (13.87%)
occurrences (all)	100	27	52
Rash maculo-papular			
subjects affected / exposed	18 / 322 (5.59%)	3 / 304 (0.99%)	8 / 310 (2.58%)
occurrences (all)	20	3	9
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	2 / 322 (0.62%)	17 / 304 (5.59%)	12 / 310 (3.87%)
occurrences (all)	2	21	13
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	44 / 322 (13.66%)	1 / 304 (0.33%)	23 / 310 (7.42%)
occurrences (all)	45	1	24
Hyperthyroidism			
subjects affected / exposed	20 / 322 (6.21%)	1 / 304 (0.33%)	7 / 310 (2.26%)
occurrences (all)	22	1	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	28 / 322 (8.70%)	13 / 304 (4.28%)	19 / 310 (6.13%)
occurrences (all)	33	15	20
Back pain			
subjects affected / exposed	21 / 322 (6.52%)	15 / 304 (4.93%)	12 / 310 (3.87%)
occurrences (all)	22	15	15
Infections and infestations			
Pneumonia			
subjects affected / exposed	37 / 322 (11.49%)	30 / 304 (9.87%)	33 / 310 (10.65%)
occurrences (all)	41	32	39
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	9 / 322 (2.80%)	5 / 304 (1.64%)	18 / 310 (5.81%)
occurrences (all)	15	8	28
Hypoalbuminaemia			
subjects affected / exposed	34 / 322 (10.56%)	20 / 304 (6.58%)	25 / 310 (8.06%)
occurrences (all)	54	28	34
Hyperkalaemia			

subjects affected / exposed	12 / 322 (3.73%)	22 / 304 (7.24%)	20 / 310 (6.45%)
occurrences (all)	13	33	27
Hypercalcaemia			
subjects affected / exposed	11 / 322 (3.42%)	9 / 304 (2.96%)	20 / 310 (6.45%)
occurrences (all)	13	12	24
Decreased appetite			
subjects affected / exposed	70 / 322 (21.74%)	156 / 304 (51.32%)	161 / 310 (51.94%)
occurrences (all)	88	296	299
Hypophosphataemia			
subjects affected / exposed	14 / 322 (4.35%)	4 / 304 (1.32%)	17 / 310 (5.48%)
occurrences (all)	16	8	19
Hyponatraemia			
subjects affected / exposed	32 / 322 (9.94%)	36 / 304 (11.84%)	55 / 310 (17.74%)
occurrences (all)	48	49	77
Hypokalaemia			
subjects affected / exposed	34 / 322 (10.56%)	30 / 304 (9.87%)	44 / 310 (14.19%)
occurrences (all)	55	56	70

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2016	Expansion of the esophageal cohort into a 3-arm randomized Phase 3 study in first line squamous esophageal cancer. The study now includes a nivolumab plus chemotherapy arm (fluorouracil and cisplatin) and a chemotherapy alone arm in addition to the existing nivolumab and ipilimumab arm. The gastric cohort was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported