Clinical trial results:
A Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

Summary

EudraCT number	2014-003698-41
Trial protocol	SE EE LV DK FI AT CZ NL HU ES RO GR DE IT GB PL
Global end of trial date	19 July 2023

Results information

Result version number	v1 (current)
This version publication date	23 June 2024
First version publication date	23 June 2024

Trial information

Trial identification

Sponsor protocol code	MK-3475-048

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02358031
WHO universal trial number (UTN)	-
Other trial identifiers	Merck: KEYNOTE-048

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2019
Global end of trial reached?	Yes
Global end of trial date	19 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Participants with recurrent or metastatic (R/M) squamous cell cancer of the head and neck (HNSCC) will be randomly assigned to receive pembrolizumab monotherapy [pembro mono], pembrolizumab plus chemotherapy with a platinum-based drug (cisplatin or carboplatin) and 5-Fluorouracil (5-FU) [pembro combo], or cetuximab plus a platinum-based drug (cisplatin or carboplatin) and 5-FU [control]. The overall primary study hypotheses are as follows in all participants and in participants with Programmed Cell Death Ligand 1 (PD-L1) positive expression defined by Combined Positive Score (CPS) ≥1 and CPS ≥20: 1) pembrolizumab monotherapy prolongs progression free survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by Blinded Independent Central Review (BICR), prolongs overall survival (OS) compared to standard treatment, and 2) pembrolizumab combination therapy prolongs PFS per RECIST 1.1 by BICR and prolongs OS compared to standard treatment.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 13
Country: Number of subjects enrolled	Australia: 51
Country: Number of subjects enrolled	Austria: 33
Country: Number of subjects enrolled	Brazil: 81
Country: Number of subjects enrolled	Canada: 39
Country: Number of subjects enrolled	Chile: 9
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Czechia: 26
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Greece: 19
Country: Number of subjects enrolled	Hong Kong: 1

Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Japan: 67
Country: Number of subjects enrolled	Latvia: 14
Country: Number of subjects enrolled	Malaysia: 12
Country: Number of subjects enrolled	Mexico: 27
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Norway: 16
Country: Number of subjects enrolled	Peru: 3
Country: Number of subjects enrolled	Philippines: 20
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	South Africa: 13
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	Switzerland: 16
Country: Number of subjects enrolled	Taiwan: 37
Country: Number of subjects enrolled	Thailand: 28
Country: Number of subjects enrolled	Türkiye: 26
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 131
Worldwide total number of subjects	882
EEA total number of subjects	254

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)	565
From 65 to 84 years	315
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants with first line recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) were recruited to examine the efficacy and safety of pembrolizumab monotherapy (pembro mono) versus pembrolizumab plus chemotherapy (pembro combo) versus cetuximab plus chemotherapy (control).

Pre-assignment

Screening details:

Of 1228 participants screened, 882 were randomized: pembro mono, pembro combo, or control arms. 22 participants in the control arm enrolled during an enrollment pause of pembro combo arm and were omitted from efficacy analyses between the respective arms. Per protocol, second course events were not included in efficacy or safety endpoints.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab Monotherapy (Pembro Mono)

Arm description:

Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle for up to 35 cycles (up to ~2 years). Qualified participants who received the first course of pembrolizumab but continued to experience disease progression may have, at the investigator’s discretion, initiated a second course of pembrolizumab at the same dose and schedule of 200 mg IV on Day 1 of each 3-week cycle for up to 17 cycles (up to ~1 year).

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA®, MK-3475
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg intravenously (IV) on Day 1 of each 3-week cycle for up to 35 cycles (up to ~2 years)

Arm title	Pembrolizumab + Chemotherapy (Pembro Combo)

Arm description:

Participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle for up to 35 cycles (up to ~2 years); plus cisplatin 100 mg/m^2 IV or carboplatin at a target area under the curve of 5 (AUC 5) IV, per Investigator's choice, on Day 1 of each 3-week cycle (6 cycle maximum [up to ~4 months]); plus 5-Fluorouracil (5-FU) 1000 mg/m^2/day IV continuous from Day 1-4 of each 3-week cycle (6 cycle maximum [up to ~4 months]). Qualified participants who received the first course of pembrolizumab but continued to experience disease progression may have, at the investigator’s discretion, initiated a second course of pembrolizumab at the same dose and schedule of 200 mg IV on Day 1 of each 3-week cycle for up to 17 cycles (up to ~1 year).

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA®, MK-3475
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg IV on Day 1 of each 3-week cycle for up to 35 cycles (up to ~2 years)

Investigational medicinal product name	5-Fluorouracil (5-FU)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m^2/day IV continuous from Day 1-4 of each 3-week cycle (6 cycle maximum [up to ~4 months])

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

Dosage and administration details:

Carboplatin at a target Area Under the Curve of 5 (AUC 5) IV on Day 1 of each 3-week cycle (6 cycle maximum [up to ~4 months])

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

Dosage and administration details:

100 mg/m^2 IV Day 1 of each 3-week cycle (6 cycle maximum [up to ~4 months])

Arm title	Cetuximab + Chemotherapy (Control)

Arm description:

Participants received cetuximab on Day 1 at a dose of 400 mg/m^2 IV, and then 250 mg/m^2 IV on Day 1 of each subsequent week until disease progression or unacceptable toxicity; plus cisplatin 100 mg/m^2 IV or carboplatin AUC 5 IV (Investigator's choice) on Day 1 of each 3-week cycle (6 cycle maximum [up to ~4 months] for platinum-based therapy); plus 5-FU 1000 mg/m^2/day IV continuous from Day 1-4 of each 3-week cycle (6 cycle maximum [up to ~4 months]).

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

Dosage and administration details:

Day 1 at a dose of 400 mg/m^2 IV, and then 250 mg/m^2 IV on Day 1 of each subsequent week until disease progression or unacceptable toxicity

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m^2/day IV continuous from Day 1-4 of each 3-week cycle (6 cycle maximum [up to ~4 months])

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

Dosage and administration details: AUC 5 IV Day 1 of each 3-week cycle (6 cycle maximum [up to ~4 months])	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 100 mg/m^2 IV Day 1 of each 3-week cycle (6 cycle maximum [up to ~4 months])	

Number of subjects in period 1	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)
Started	301	281	300
Treated	300	276	287
Pembro Mono v Control Efficacy Analyses	301	0 [1]	300
Pembro Combo v Control Efficacy Analyses	0 [2]	281	278
Received Second Course of Pembrolizumab	8	6	0
Completed	2	1	0
Not completed	299	280	300
Consent withdrawn by subject	19	14	18
Death	253	237	266
Sponsor Decision	26	28	16
Lost to follow-up	1	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Per protocol, efficacy analyses were performed by comparing the Pembro Combo arm versus the Control arm. Due to a pause in enrollment in the Pembro Combo arm, only the concurrent control arm is used for their comparison.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Per protocol, efficacy analyses were performed by comparing the Pembro Mono arm versus the Control arm. Due to a pause in enrollment in the Pembro Combo arm, only the concurrent control arm is used for their comparison.

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab Monotherapy (Pembro Mono)
Reporting group description:	
Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle for up to 35 cycles (up to ~2 years). Qualified participants who received the first course of pembrolizumab but continued to experience disease progression may have, at the investigator's discretion, initiated a second course of pembrolizumab at the same dose and schedule of 200 mg IV on Day 1 of each 3-week cycle for up to 17 cycles (up to ~1 year).	
Reporting group title	Pembrolizumab + Chemotherapy (Pembro Combo)
Reporting group description:	
Participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle for up to 35 cycles (up to ~2 years); plus cisplatin 100 mg/m^2 IV or carboplatin at a target area under the curve of 5 (AUC 5) IV, per Investigator's choice, on Day 1 of each 3-week cycle (6 cycle maximum [up to ~4 months]); plus 5-Fluorouracil (5-FU) 1000 mg/m^2/day IV continuous from Day 1-4 of each 3-week cycle (6 cycle maximum [up to ~4 months]). Qualified participants who received the first course of pembrolizumab but continued to experience disease progression may have, at the investigator's discretion, initiated a second course of pembrolizumab at the same dose and schedule of 200 mg IV on Day 1 of each 3-week cycle for up to 17 cycles (up to ~1 year).	
Reporting group title	Cetuximab + Chemotherapy (Control)
Reporting group description:	
Participants received cetuximab on Day 1 at a dose of 400 mg/m^2 IV, and then 250 mg/m^2 IV on Day 1 of each subsequent week until disease progression or unacceptable toxicity; plus cisplatin 100 mg/m^2 IV or carboplatin AUC 5 IV (Investigator's choice) on Day 1 of each 3-week cycle (6 cycle maximum [up to ~4 months] for platinum-based therapy); plus 5-FU 1000 mg/m^2/day IV continuous from Day 1-4 of each 3-week cycle (6 cycle maximum [up to ~4 months]).	

Reporting group values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)
Number of subjects	301	281	300
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)	190	180	195
From 65-84 years	110	100	105
85 years and over	1	1	0
Age Continuous Units: Years			
arithmetic mean	61.2	60.7	61.0
standard deviation	± 9.4	± 9.8	± 10.0
Sex: Female, Male Units: Participants			
Female	51	57	39
Male	250	224	261

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	5	3	6
Asian	58	60	54
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	11	6
White	219	203	224
More than one race	12	4	9
Unknown or Not Reported	3	0	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	46	45	44
Not Hispanic or Latino	233	213	231
Unknown or Not Reported	22	23	25
Eastern Cooperative Group (ECOG) Performance Status			
An ECOG Performance Status of 0 (Fully active, able to carry on all pre-disease performance without restriction) or 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature) was required for inclusion in the trial.			
Units: Subjects			
ECOG = 0	118	110	117
ECOG = 1	183	171	183
Human Papillomavirus (HPV) Status			
HPV status for oropharynx cancer as determined by p16 immunohistochemistry (IHC) (positive vs. negative); HPV status for participants without oropharynx cancer was considered HPV negative.			
Units: Subjects			
HPV Positive	63	60	67
HPV Negative	238	221	233
PD-L1 TPS Status			
The Programmed Cell Death Ligand 1 (PD-L1) Tumor Proportion Score (TPS) Status indicates the degree by which participants tumors stain positive for PD-L1 by IHC staining (i.e. strongly positive or not strongly positive). Participants with a TPS ≥50% were classified as PD-L1 "strongly positive" and participants with a TPS <50% were classified as "not strongly positive."			
Units: Subjects			
Strongly Positive	67	66	66
Not Strongly Positive	234	215	234
PD-L1 CPS ≥1 Status			
The PD-L1 Combined Positive Score (CPS) Status indicates tumor PD-L1 positivity using both tumor cells and inflammatory cells that are positive for PD-L1 by IHC. The number of participants with CPS<1 and CPS≥1 at baseline is presented. Participants with a CPS<1 were classified as PD-L1 negative and participants with a CPS≥1 were classified as PD-L1 positive.			
Units: Subjects			
CPS<1	44	39	45
CPS ≥1	257	242	255
PD-L1 CPS ≥20 Status			
The PD-L1 CPS Status indicates tumor PD-L1 positivity using both tumor cells and inflammatory cells that are positive for PD-L1 by IHC. The number of participants with CPS<20 and CPS ≥20 at baseline is presented.			
Units: Subjects			
CPS <20	167	154	175
CPS ≥20	133	126	122
Missing	1	1	3

Reporting group values	Total		

Number of subjects	882		
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)	565		
From 65-84 years	315		
85 years and over	2		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	147		
Male	735		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	14		
Asian	172		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	21		
White	646		
More than one race	25		
Unknown or Not Reported	4		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	135		
Not Hispanic or Latino	677		
Unknown or Not Reported	70		
Eastern Cooperative Group (ECOG) Performance Status			
An ECOG Performance Status of 0 (Fully active, able to carry on all pre-disease performance without restriction) or 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature) was required for inclusion in the trial.			
Units: Subjects			
ECOG = 0	345		
ECOG = 1	537		
Human Papillomavirus (HPV) Status			
HPV status for oropharynx cancer as determined by p16 immunohistochemistry (IHC) (positive vs. negative); HPV status for participants without oropharynx cancer was considered HPV negative.			
Units: Subjects			
HPV Positive	190		
HPV Negative	692		
PD-L1 TPS Status			
The Programmed Cell Death Ligand 1 (PD-L1) Tumor Proportion Score (TPS) Status indicates the degree by which participants tumors stain positive for PD-L1 by IHC staining (i.e. strongly positive or not			

strongly positive). Participants with a TPS ≥50% were classified as PD-L1 "strongly positive" and participants with a TPS <50% were classified as "not strongly positive."			
Units: Subjects			
Strongly Positive	199		
Not Strongly Positive	683		
PD-L1 CPS ≥1 Status			
The PD-L1 Combined Positive Score (CPS) Status indicates tumor PD-L1 positivity using both tumor cells and inflammatory cells that are positive for PD-L1 by IHC. The number of participants with CPS<1 and CPS≥1 at baseline is presented. Participants with a CPS<1 were classified as PD-L1 negative and participants with a CPS≥1 were classified as PD-L1 positive.			
Units: Subjects			
CPS<1	128		
CPS ≥1	754		
PD-L1 CPS ≥20 Status			
The PD-L1 CPS Status indicates tumor PD-L1 positivity using both tumor cells and inflammatory cells that are positive for PD-L1 by IHC. The number of participants with CPS<20 and CPS ≥20 at baseline is presented.			
Units: Subjects			
CPS <20	496		
CPS ≥20	381		
Missing	5		

End points

End points reporting groups

Reporting group title	Pembrolizumab Monotherapy (Pembro Mono)
Reporting group description:	
Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle for up to 35 cycles (up to ~2 years). Qualified participants who received the first course of pembrolizumab but continued to experience disease progression may have, at the investigator's discretion, initiated a second course of pembrolizumab at the same dose and schedule of 200 mg IV on Day 1 of each 3-week cycle for up to 17 cycles (up to ~1 year).	
Reporting group title	Pembrolizumab + Chemotherapy (Pembro Combo)
Reporting group description:	
Participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle for up to 35 cycles (up to ~2 years); plus cisplatin 100 mg/m^2 IV or carboplatin at a target area under the curve of 5 (AUC 5) IV, per Investigator's choice, on Day 1 of each 3-week cycle (6 cycle maximum [up to ~4 months]); plus 5-Fluorouracil (5-FU) 1000 mg/m^2/day IV continuous from Day 1-4 of each 3-week cycle (6 cycle maximum [up to ~4 months]). Qualified participants who received the first course of pembrolizumab but continued to experience disease progression may have, at the investigator's discretion, initiated a second course of pembrolizumab at the same dose and schedule of 200 mg IV on Day 1 of each 3-week cycle for up to 17 cycles (up to ~1 year).	
Reporting group title	Cetuximab + Chemotherapy (Control)
Reporting group description:	
Participants received cetuximab on Day 1 at a dose of 400 mg/m^2 IV, and then 250 mg/m^2 IV on Day 1 of each subsequent week until disease progression or unacceptable toxicity; plus cisplatin 100 mg/m^2 IV or carboplatin AUC 5 IV (Investigator's choice) on Day 1 of each 3-week cycle (6 cycle maximum [up to ~4 months] for platinum-based therapy); plus 5-FU 1000 mg/m^2/day IV continuous from Day 1-4 of each 3-week cycle (6 cycle maximum [up to ~4 months]).	

Primary: Pembro Combo vs Control: Progression Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by Blinded Independent Central Review (BICR) in All Participants

End point title	Pembro Combo vs Control: Progression Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by Blinded Independent Central Review (BICR) in All Participants
End point description:	
PFS is the time from randomization to first documented progressive disease (PD) per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the sum of diameters (SOD) of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol PFS in the pembro combo versus the control arm was a pre-specified primary analysis of the Intent-To-Treat (ITT) population, consisting of all randomized participants during active enrollment. 22 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. PFS is reported here for the first course, for all participants in the pembro combo and control arm. Per protocol PFS was compared separately between all participants of the pembro mono and control arm and is presented later.	
End point type	Primary
End point timeframe:	
Up to approximately 47 months	

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[1]	281	278	
Units: Months				
median (confidence interval 95%)	(to)	4.9 (4.7 to 6.1)	5.2 (4.9 to 6.1)	

Notes:

[1] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	PFS in All Participants

Statistical analysis description:

PFS in all participants of the pembro combo arm was compared to PFS in all participants of the control arm to address the sixth primary hypothesis. The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status.

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21211 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.11

Notes:

[2] - One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status.

Primary: Pembro Combo vs Control: PFS per RECIST 1.1 by BICR in Participants With Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) ≥1

End point title	Pembro Combo vs Control: PFS per RECIST 1.1 by BICR in Participants With Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) ≥1

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurrs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro combo versus the control arm was a pre-specified primary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by immunohistochemistry (IHC) as Combined Positive Score ≥1 (CPS ≥1). 12 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. PFS is reported here for the first course of treatment, for all participants in the pembro combo and control arm with CPS ≥1. Per protocol, PFS was compared separately between CPS ≥1 participants of the pembro mono arm and control arm and is presented later.

End point type	Primary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[3]	242	235	
Units: Months				
median (confidence interval 95%)	(to)	5.1 (4.7 to 6.2)	5.0 (4.8 to 6.0)	

Notes:

[3] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	PFS in participants with CPS≥1

Statistical analysis description:

PFS in CPS ≥1 participants of the pembro combo arm was compared to PFS in CPS ≥1 participants of the control arm to address the fifth primary hypothesis. The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status.

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03697 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.02

Notes:

[4] - One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status.

Primary: Pembro Combo vs Control: PFS per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥20

End point title	Pembro Combo vs Control: PFS per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥20

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro combo arm versus the control arm was a pre-specified primary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as Combined Positive Score ≥20 (CPS ≥20). 12 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. PFS is reported here for the first course, for all participants in the pembro combo and control arm with CPS ≥20. Per protocol, PFS was compared separately between CPS ≥20 participants of the pembro mono and control arm and is presented later.

End point type	Primary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	126	110	
Units: Months				
median (confidence interval 95%)	(to)	5.8 (4.7 to 7.6)	5.3 (4.9 to 6.3)	

Notes:

[5] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	PFS in participants with CPS≥20

Statistical analysis description:

PFS in CPS ≥20 participants of the pembro combo arm was compared to PFS in CPS ≥20 participants of the control arm to address the fourth primary hypothesis. The comparison was based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by ECOG and HPV status.

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02951 [6]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.01

Notes:

[6] - One-sided p-value based on log-rank test stratified by ECOG and HPV status.

Primary: Pembro Combo vs Control: Overall Survival (OS) in All Participants

End point title	Pembro Combo vs Control: Overall Survival (OS) in All Participants

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro combo arm versus the control arm was a pre-specified primary analysis of the ITT population, consisting of all randomized participants during active enrollment. 22 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. OS is reported here for the first course, for all participants in the pembro combo and control arm. Per protocol, OS was compared separately between all participants of the pembro mono arm and control

arm and is presented later.

End point type	Primary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[7]	281	278	
Units: Months				
median (confidence interval 95%)	(to)	13.0 (10.9 to 14.7)	10.7 (9.3 to 11.7)	

Notes:

[7] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	OS in All Participants

Statistical analysis description:

OS in all participants of the pembro combo arm was compared to OS in all participants of the control arm to address the fourteenth primary hypothesis. The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status.

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00025 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.87

Notes:

[8] - One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status.

Primary: Pembro Combo vs Control: OS in Participants With PD-L1 CPS ≥1

End point title	Pembro Combo vs Control: OS in Participants With PD-L1 CPS ≥1

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro combo arm versus the control arm was a pre-specified primary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS≥1. 20 participants in the control arm enrolled

during an enrollment pause of the pembro combo arm were excluded. OS is reported here for the first course, for all participants in the pembro combo arm and control arm with PD-L1 biomarker positive expression defined by IHC as CPS ≥1. Per protocol, OS was compared separately between CPS ≥1 participants of the pembro mono arm and control arm and is presented later.

End point type	Primary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[9]	242	235	
Units: Months				
median (confidence interval 95%)	(to)	13.6 (10.7 to 15.5)	10.4 (9.1 to 11.7)	

Notes:

[9] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	OS in participants with CPS≥1

Statistical analysis description:

OS in CPS ≥1 participants of the pembro combo arm was compared to OS in CPS ≥1 participants of the control arm to address the twelfth primary hypothesis. The comparison was based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status.

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.8

Notes:

[10] - p-value = 0.00002; One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status.

Primary: Pembro Combo vs Control: OS in Participants With PD-L1 CPS ≥20

End point title	Pembro Combo vs Control: OS in Participants With PD-L1 CPS ≥20

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per

protocol, OS in the pembro combo arm versus the control arm was a pre-specified primary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS≥20. 12 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. OS is reported here for the first course, for all participants in the pembro combo and control arm with CPS≥20. Per protocol, OS was compared separately between CPS ≥20 participants of the pembro mono arm and control arm and is presented later.

End point type	Primary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[11]	126	110	
Units: Months				
median (confidence interval 95%)	(to)	14.7 (10.3 to 19.3)	11.0 (9.2 to 13.0)	

Notes:

[11] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	OS in participants with CPS≥20

Statistical analysis description:

OS in CPS ≥20 participants of the pembro combo arm was compared to OS in CPS ≥20 participants of the control arm to address the eleventh primary hypothesis. The comparison was based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by ECOG and HPV status.

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00044 [12]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.82

Notes:

[12] - One-sided p-value based on log-rank test stratified by ECOG and HPV status.

Primary: Pembro Mono vs Control: PFS per RECIST 1.1 by BICR in All Participants

End point title	Pembro Mono vs Control: PFS per RECIST 1.1 by BICR in All Participants

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro mono arm versus the control arm was a pre-specified primary analysis of the ITT population, consisting of all randomized participants during active enrollment. PFS is reported here for the first course, for all participants in the pembro mono arm and control arm. Per protocol, PFS was compared separately between all participants of the pembro combo arm and control arm and is presented earlier.

End point type	Primary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	301	0[13]	300	
Units: Months				
median (confidence interval 95%)	2.3 (2.2 to 3.3)	(to)	5.2 (4.9 to 6.1)	

Notes:

[13] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	PFS in All Participants

Statistical analysis description:

PFS in all participants of the pembro mono arm was compared to PFS in all participants of the control arm to address the third primary hypothesis. The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	601
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9983 [14]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	1.53

Notes:

[14] - One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status.

Primary: Pembro Mono vs Control: PFS per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1

End point title	Pembro Mono vs Control: PFS per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 lesions is also PD. Per protocol, PFS in the pembro mono arm versus the control arm was a pre-specified primary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥1. PFS is reported here for the first course, for all participants in the pembro mono and control arm with CPS≥1. Per protocol, PFS was compared separately between CPS ≥1 participants of the pembro combo arm and control arm and is presented earlier.

End point type	Primary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	257	0[15]	255	
Units: Months				
median (confidence interval 95%)	3.2 (2.2 to 3.4)	(to)	5.0 (4.8 to 6.0)	

Notes:

[15] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	PFS in participants with CPS≥1

Statistical analysis description:

PFS in CPS ≥1 participants of the pembro mono arm was compared to PFS in CPS ≥1 participants of the control arm to address the second primary hypothesis. The comparison was based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8958 [16]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.36

Notes:

[16] - One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status.

Primary: Pembro Mono vs Control: PFS per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥20

End point title	Pembro Mono vs Control: PFS per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥20

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro mono arm versus the control arm was a pre-specified primary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥20. PFS is reported here for the first course, for all participants in the pembro mono and control arm with CPS ≥20. Per protocol, PFS was compared separately between CPS ≥20 participants of the pembro combo arm and control arm and is presented earlier.

End point type	Primary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	0[17]	122	
Units: Months				
median (confidence interval 95%)	3.4 (3.2 to 3.8)	(to)	5.3 (4.8 to 6.3)	

Notes:

[17] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	PFS in participants with CPS≥20

Statistical analysis description:

PFS in CPS ≥20 participants of the pembro mono arm was compared to PFS in CPS ≥20 participants of the control arm to address the first primary hypothesis. The comparison was based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by ECOG and HPV status.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46791 [18]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.29

Notes:

[18] - One-sided p-value based on log-rank test stratified by ECOG and HPV status.

Primary: Pembro Mono vs Control: OS in All Participants

End point title	Pembro Mono vs Control: OS in All Participants

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro mono arm versus the control arm was a pre-specified primary analysis of the ITT population, consisting of all randomized participants during active enrollment. OS is reported here for the first course, for all participants in the pembro mono and control arm. Per protocol, OS was compared separately between all participants of the pembro combo arm and control arm and is presented earlier.

End point type	Primary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	301	0[19]	300	
Units: Months				
median (confidence interval 95%)	11.5 (10.3 to 13.4)	(to)	10.7 (9.3 to 11.7)	

Notes:

[19] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	OS in All Participants

Statistical analysis description:

OS in all participants of the pembro mono arm was compared to OS in all participants of the control arm to address the tenth primary hypothesis. The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	601
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01985 [20]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.99

Notes:

[20] - One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status.

Primary: Pembro Mono vs Control: OS in Participants With PD-L1 CPS ≥1

End point title	Pembro Mono vs Control: OS in Participants With PD-L1 CPS ≥1

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro mono arm versus the control arm was a pre-specified primary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥1. OS is reported here for the first course, for all participants in the pembro mono and control arm with CPS ≥1. Per protocol, OS was compared separately between CPS ≥1 participants of the pembro combo arm and control arm and is presented earlier.

End point type	Primary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	257	0[21]	255	
Units: Months				
median (confidence interval 95%)	12.3 (10.8 to 14.3)	(to)	10.3 (9.0 to 11.5)	

Notes:

[21] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	OS in participants with CPS≥1

Statistical analysis description:

OS in CPS ≥1 participants of the pembro mono arm was compared to OS in CPS ≥1 participants of the control arm to address the eighth primary hypothesis. The comparison was based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00133 [22]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.9

Notes:

[22] - One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status.

Primary: Pembro Mono vs Control: OS in Participants With PD-L1 CPS ≥20

End point title	Pembro Mono vs Control: OS in Participants With PD-L1 CPS ≥20

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. Per protocol, OS in the pembro mono arm versus the control arm was a pre-specified primary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥20. OS is reported here for the first course, for all participants in the pembro mono arm and control arm with CPS ≥20. Per protocol, OS was compared separately between CPS ≥20 participants of the pembro combo arm and control arm and is presented earlier.

End point type	Primary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	0[23]	122	
Units: Months				
median (confidence interval 95%)	14.8 (11.5 to 20.6)	(to)	10.7 (8.8 to 12.8)	

Notes:

[23] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	OS in participants with CPS≥20

Statistical analysis description:

OS in CPS ≥20 participants of the pembro mono arm was compared to OS in CPS ≥20 participants of the control arm to address the seventh primary hypothesis. The comparison was based on a Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by ECOG and HPV status.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab + Chemotherapy (Control)

Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [24]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.78

Notes:

[24] - One-sided p-value based on log-rank test stratified by ECOG and HPV status.

Secondary: Pembro Combo vs Control: Percentage of Participants with PFS at 6 Months per RECIST 1.1 by BICR Among All Participants

End point title	Pembro Combo vs Control: Percentage of Participants with PFS at 6 Months per RECIST 1.1 by BICR Among All Participants

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro combo arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment. 22 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. The percentage of participants with PFS (PFS rate) at 6 months is reported here, for the first course, for all participants in the pembro combo arm and control arm. Per protocol, the percentage of participants with PFS at 6 months was compared separately between all participants of the pembro mono arm and control arm and is presented later.

End point type	Secondary

End point timeframe:

Month 6

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[25]	281	278	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	44.7 (38.8 to 50.5)	44.9 (38.9 to 50.8)	

Notes:

[25] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Combo vs Control: Percentage of Participants with PFS at 6

Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥1

End point title	Pembro Combo vs Control: Percentage of Participants with PFS at 6 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥1

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro combo versus control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥1. 20 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. The percentage of participants with PFS (PFS rate) at 6 months is reported here, for the first course, for all participants in the pembro combo and control arm with CPS ≥1. Per protocol, PFS rate at 6 months was compared separately between CPS ≥1 participants of the pembro mono arm and control arm and is presented later.

End point type	Secondary

End point timeframe:

Month 6

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[26]	242	235	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	44.9 (38.5 to 51.1)	43.3 (36.9 to 49.6)	

Notes:

[26] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Combo vs Control: Percentage of Participants with PFS at 6 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥20

End point title	Pembro Combo vs Control: Percentage of Participants with PFS at 6 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥20

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro combo arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥20. 12 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. The percentage of participants with PFS (PFS rate) at 6 months is reported here, for the first course, for all participants in the pembro combo and control arm with CPS≥20. Per protocol, PFS rate at 6 months was compared separately between CPS ≥20 participants of the pembro mono and control arm and is presented later.

End point type	Secondary

End point timeframe:

Month 6

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[27]	126	110	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	49.4 (40.3 to 57.9)	47.2 (37.5 to 56.2)	

Notes:

[27] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Combo vs Control: Percentage of Participants with PFS at 12 Months per RECIST 1.1 by BICR Among All Participants

End point title	Pembro Combo vs Control: Percentage of Participants with PFS at 12 Months per RECIST 1.1 by BICR Among All Participants

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro combo arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment. 22 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. The percentage of participants with PFS (PFS rate) at 12 months is reported here, for the first course, for all participants in the pembro combo and control arm. Per protocol, the percentage of participants with PFS at 12 months was compared separately between all participants of the pembro mono and control arm and is presented later.

End point type	Secondary

End point timeframe:

Month 12

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[28]	281	278	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	17.2 (13.0 to 21.9)	13.6 (9.8 to 18.1)	

Notes:

[28] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Combo vs Control: Percentage of Participants with PFS at 12 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥1

End point title	Pembro Combo vs Control: Percentage of Participants with PFS at 12 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥1

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro combo arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥1. 20 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. The percentage of participants with PFS (PFS rate) at 12 months is reported here, for the first course, for all participants with in the pembro combo arm and control arm with CPS≥1. Per protocol, PFS rate at 12 months was compared separately between CPS ≥1 participants of the pembro mono arm and control arm and is presented later.

End point type	Secondary

End point timeframe:

Month 12

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[29]	242	235	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	19.7 (14.8 to 25.0)	12.5 (8.6 to 17.3)	

Notes:

[29] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Combo vs Control: Percentage of Participants with PFS at 12 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥20

End point title	Pembro Combo vs Control: Percentage of Participants with PFS at 12 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥20

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro combo arm versus control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥20. 12 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. The percentage of participants with PFS (PFS rate) at 12 months is reported here, for the first course, for all participants in the pembro combo and control arm with CPS ≥20. Per protocol, PFS rate at 12 months was compared separately between

CPS ≥20 participants of the pembro mono and control arm and is presented later.

End point type	Secondary

End point timeframe:

Month 12

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[30]	126	110	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	23.9 (16.7 to 31.7)	14.0 (8.2 to 21.3)	

Notes:

[30] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Combo vs Control: Objective Response Rate (ORR) per RECIST 1.1 by BICR in All Participants

End point title	Pembro Combo vs Control: Objective Response Rate (ORR) per RECIST 1.1 by BICR in All Participants

End point description:

ORR was defined as the percentage of participants in the analysis population who have a Complete Response (CR: disappearance of all target lesions) or a Partial Response (PR: ≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1. by BICR. Per protocol, ORR in the pembro combo arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment. 22 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. The percentage of participants who experienced CR or PR is reported here as the ORR, for the first course, for all participants in the pembro combo arm and control arm. Per protocol, ORR was compared separately between all participants of the pembro mono arm and control arm and is presented later.

End point type	Secondary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[31]	281	278	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	35.6 (30.0 to 41.5)	36.3 (30.7 to 42.3)	

Notes:

[31] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	ORR in all participants

Statistical analysis description:

ORR in all participants of the pembro combo arm was compared to ORR in all participants of the control arm. The comparison was based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 TPS status (Strongly Positive, Not Strongly Positive).

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.574 [32]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in ORR Percentage
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	7.2

Notes:

[32] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Combo vs Control: ORR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1

End point title	Pembro Combo vs Control: ORR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1

End point description:

ORR was defined as the percentage of participants in the analysis population who have a CR (disappearance of all target lesions) or a PR (≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1. by BICR. Per protocol, ORR in the pembro combo arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥1. 20 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. The percentage of participants who experienced CR or PR is reported here as the ORR, for the first course, for all participants in the pembro combo arm and control arm with CPS ≥1. Per protocol, ORR was compared separately between CPS ≥1 participants of the pembro mono arm and control arm and is presented later.

End point type	Secondary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[33]	242	235	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	36.4 (30.3 to 42.8)	35.7 (29.6 to 42.2)	

Notes:

[33] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	ORR in participants with CPS≥1

Statistical analysis description:

ORR in CPS ≥1 participants of the pembro combo arm was compared to ORR in CPS ≥1 participants of the control arm. The comparison was based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 TPS status (Strongly Positive, Not Strongly Positive).

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4586 [34]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in ORR Percentage
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	9.1

Notes:

[34] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Combo vs Control: Change From Baseline to Week 15 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status/Quality of Life (Items 29 and 30) Combined Score

End point title	Pembro Combo vs Control: Change From Baseline to Week 15 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status/Quality of Life (Items 29 and 30) Combined Score

End point description:

EORTC-QLQ-C30 is a 30-item questionnaire to assess the quality of life (QoL) of cancer patients. Responses to "How would you rate your overall health during the past week?" (Item 29) and "How would you rate your overall quality of life during the past week?" (Item 30) were scored on a 7-point scale (1=Very Poor to 7=Excellent). Raw scores were standardized so scores ranged from 0 to 100; a higher score indicating a better overall outcome. Per protocol change from baseline (BL) to Week 15 in GHS/QoL combined score, for the first course, in all participants of the pembro combo versus control arm was a pre-specified secondary analysis; and compared separately between all participants of pembro mono and control arm, as presented later. All participants in the pembro combo and control arm who got ≥1 dose of study drug and had assessments available at- or post-BL up to Week 15 were analyzed. 20 in the control arm in an enrollment pause of pembro combo arm were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[35]	268	259	
Units: Score on a Scale				
least squares mean (confidence interval 95%)	(to)	1.17 (-1.79 to 4.12)	0.77 (-2.22 to 3.76)	

Notes:

[35] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	Change from Baseline: EORTC QLQ-C30 Items 29 & 30

Statistical analysis description:

Change from baseline to Week 15 in EORTC-QLQ-C30 GHS/QoL combined score was compared between all participants of the pembro combo arm and the control arm. Comparison based on constrained longitudinal data analysis (cLDA) model with GHS/QoL score as response variable and treatment by visit interaction, stratification factors (ECOG [0 vs. 1], HPV status [Positive vs. Negative] and PD-L1 TPS status [Strongly Positive, Not Strongly Positive]) as covariates.

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.839 [36]
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.46
upper limit	4.26

Notes:

[36] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Combo vs Control: ORR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥20

End point title	Pembro Combo vs Control: ORR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥20

End point description:

ORR was defined as the percentage of participants in the analysis population who have a CR (disappearance of all target lesions) or a PR (≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1. by BICR. Per protocol, ORR in the pembro combo arm versus the control arm as a pre-specified secondary analysis of the ITT population, consisting of consisting of all randomized participants

during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥20. 12 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. The percentage of participants who experienced CR or PR is reported here as the ORR, for the first course, for all participants in the pembro combo arm and control arm with CPS≥20. Per protocol, ORR was compared separately between CPS ≥20 participants of the pembro mono arm and control arm and is presented later.

End point type	Secondary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[37]	126	110	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	42.9 (34.1 to 52.0)	38.2 (29.1 to 47.9)	

Notes:

[37] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	ORR in participants with CPS≥20

Statistical analysis description:

ORR in CPS ≥20 participants of the pembro combo arm was compared to ORR in CPS ≥20 participants of the control arm. The comparison was based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1) and HPV status (Positive vs. Negative).

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2161 [38]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in ORR Percentage
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	17.4

Notes:

[38] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Combo vs Control: Time to Deterioration (TTD) in the EORTC QLQ-C30 Global Health Status/Quality of Life (Items 29 and 30) Combined Score (Kaplan-Meier Method)

End point title	Pembro Combo vs Control: Time to Deterioration (TTD) in the EORTC QLQ-C30 Global Health Status/Quality of Life (Items 29 and 30) Combined Score (Kaplan-Meier Method)

End point description:

EORTC-QLQ-C30 is a 30-item questionnaire assessing QoL of cancer patients. Response to "How would you rate your overall health during the past week?" (Item 29) and "How would you rate your overall QoL during the past week?" (Item 30) were scored on a 7-point scale (1=Very Poor to 7=Excellent). Raw scores were standardized so scores ranged from 0 to 100; a higher score indicating a better outcome. TTD is the time from BL to first onset of a ≥10-point decrease from BL in GHS/QoL score. Per protocol TTD for the first course, in all participants of pembro combo versus control arm was a pre-specified secondary analysis; TTD in pembro mono versus control arm was presented later. All participants in the pembro combo and control arms who completed EORTC QLQ-C30 and got ≥1 dose of study drug were analyzed. 20 in the control arm enrolled during an enrollment pause of the pembro combo arm were excluded. 9999: Value not reached due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

Baseline up to approximately 12 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[39]	270	260	
Units: Months				
median (confidence interval 95%)	(to)	9999 (9999 to 9999)	9999 (9999 to 9999)	

Notes:

[39] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	TTD: EORTC QLQ-C30 Items 29 & 30

Statistical analysis description:

TTD in GHS/QoL combined score was compared between all participants of the pembro combo arm and the control arm. Comparison based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 TPS status (Strongly Positive, Not Strongly Positive).

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9497 [40]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	2

Notes:

[40] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Combo vs Control: TTD in the EORTC QLQ- Head and Neck Module 35 (H&N35) Pain Score (Kaplan-Meier Method)

End point title	Pembro Combo vs Control: TTD in the EORTC QLQ- Head and Neck Module 35 (H&N35) Pain Score (Kaplan-Meier Method)

End point description:

ORTC QLQ-H&N35 is a 35-item questionnaire to assess QoL of head and neck cancer patients (7 multi-item scales to assess pain, swallowing, senses, speech, social eating, social contact, sexuality). Responses to the Pain scale (Items 31-34) were scored on a 4-point scale (1=Not at all to 4=Very much). Raw scores were standardized so scores ranged from 0 to 100; a higher score indicating more problems. TTD is the time from BL to first onset of a ≥10-point decrease from BL. Per protocol TTD in Pain Score for first course, in all participants of pembro combo versus control arm was a pre-specified secondary analysis; TTD in pembro mono versus control arm was presented later. All participants in the pembro combo and control arm who got ≥1 dose of study drug and completed EORTC QLQ-H&N35 were analyzed, 20 participants enrolled in the control arm during an enrollment pause of the pembro combo arm were excluded. 9999: Value not reached due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

Baseline up to approximately 12 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[41]	268	260	
Units: Months				
median (confidence interval 95%)	(to)	9999 (9999 to 9999)	9999 (9999 to 9999)	

Notes:

[41] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	TTD: EORTC QLQ-H&N35 Pain Score

Statistical analysis description:

TTD in EORTC QLQ-H&N35 Pain Score was compared between all participants of the pembro combo arm and the control arm. Comparison based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 TPS status (Strongly Positive, Not Strongly Positive).

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	528
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9476 [42]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	2.02

Notes:

[42] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Combo vs Control: TTD in the EORTC QLQ- H&N35 Swallowing Score (Kaplan-Meier Method)

End point title	Pembro Combo vs Control: TTD in the EORTC QLQ- H&N35 Swallowing Score (Kaplan-Meier Method)

End point description:

EORTC QLQ-H&N35 is a 35-item questionnaire to assess QoL of head and neck cancer patients (7 multi-item scales to assess pain, swallowing, senses, speech, social eating, social contact, sexuality). Responses to Swallowing scale (Items 35-38) were scored on a 4-point scale (1=Not at all to 4=Very much). Raw scores were standardized so scores ranged from 0 to 100; a higher score indicating more problems. TTD is the time from BL to the first onset of a ≥10-point decrease from BL. Per protocol TTD for the first course, in all participants of the pembro combo versus control arm was a pre-specified secondary analysis; TTD in pembro mono versus control arm was presented later. All participants in the pembro combo and control arm who completed the EORTC QLQ-H&N35 and got ≥1 dose of study drug were analyzed; 20 enrolled in control arm during an enrollment pause of the pembro combo arm were excluded. 9999: Value not reached due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

Baseline up to approximately 12 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[43]	268	260	
Units: Months				
median (confidence interval 95%)	(to)	9999 (9999 to 9999)	9999 (9999 to 9999)	

Notes:

[43] - Per protocol, the Pembro Mono Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	TTD: EORTC QLQ-H&N35 Swallowing Score

Statistical analysis description:

TTD in EORTC QLQ-H&N35 Swallowing Score was compared between all participants of the pembro combo arm and the control arm. Comparison based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 TPS status (Strongly Positive, Not Strongly Positive).

Comparison groups	Pembrolizumab + Chemotherapy (Pembro Combo) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	528
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5836 [44]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.59

Notes:

[44] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs Control: Percentage of Participants with PFS at 6 Months per RECIST 1.1 by BICR Among All Participants

End point title	Pembro Mono vs Control: Percentage of Participants with PFS at 6 Months per RECIST 1.1 by BICR Among All Participants

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro mono arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment. The percentage of participants with PFS (PFS rate) at 6 months is reported here, for the first course, for all participants in the pembro mono arm and control arm. Per protocol, PFS rate at 6 months was compared separately between all participants of the pembro combo arm and control arm and is presented earlier.

End point type	Secondary

End point timeframe:

Month 6

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	301	0[45]	300	
Units: Percentage of Participants				
number (confidence interval 95%)	26.2 (21.4 to 31.3)	(to)	45.7 (39.9 to 51.3)	

Notes:

[45] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Mono vs Control: Percentage of Participants with PFS at 6 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥1

End point title	Pembro Mono vs Control: Percentage of Participants with PFS at 6 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥1

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro mono arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥1. The percentage of participants with PFS (PFS rate) at 6

months is reported here, for the first course, for all participants in the pembro mono arm and control arm with CPS≥1. Per protocol, the percentage of participants with PFS at 6 months was compared separately between CPS ≥1 participants of the pembro combo arm and control arm and is presented earlier.

End point type	Secondary

End point timeframe:

Month 6

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	257	0[46]	255	
Units: Percentage of Participants				
number (confidence interval 95%)	28.7 (23.3 to 34.4)	(to)	43.9 (37.6 to 49.9)	

Notes:

[46] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Mono vs Control: Percentage of Participants with PFS at 12 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥1

End point title	Pembro Mono vs Control: Percentage of Participants with PFS at 12 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥1

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro mono arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥1. The percentage of participants with PFS (PFS rate) at 12 months is reported here, for the first course, for all participants in the pembro mono and control arm with CPS≥1. Per protocol, the percentage of participants with PFS at 12 months was compared separately between CPS ≥1 participants of the pembro combo and control arm and is presented earlier.

End point type	Secondary

End point timeframe:

Month 12

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	257	0[47]	255	
Units: Percentage of Participants				

number (confidence interval 95%)	20.6 (15.9 to 25.8)	(to)	13.6 (9.6 to 18.2)	

Notes:

[47] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Mono vs Control: Percentage of Participants with PFS at 12 Months per RECIST 1.1 by BICR Among All Participants

End point title	Pembro Mono vs Control: Percentage of Participants with PFS at 12 Months per RECIST 1.1 by BICR Among All Participants

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro mono arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment. The percentage of participants with PFS (PFS rate) at 12 months is reported here, for the first course, for all participants in the pembro mono arm and control arm. Per protocol, the percentage of participants with PFS at 12 months was compared separately between all participants of the pembro combo arm and control arm and is presented earlier.

End point type	Secondary

End point timeframe:

Month 12

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	301	0[48]	300	
Units: Percentage of Participants				
number (confidence interval 95%)	17.6 (13.5 to 22.1)	(to)	15.0 (11.2 to 19.4)	

Notes:

[48] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Mono vs Control: Percentage of Participants with PFS at 6 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥20

End point title	Pembro Mono vs Control: Percentage of Participants with PFS at 6 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥20

End point description:

PFS is the time from randomization to first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an

additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro mono arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥20. The percentage of participants with PFS (PFS rate) at 6 months is reported here, for the first course, for all participants with in the pembro mono arm and control arm with CPS≥20. Per protocol, PFS rate at 6 months was compared separately between CPS ≥20 participants of the pembro combo arm and control arm and is presented earlier.

End point type	Secondary

End point timeframe:

Month 6

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	0[49]	122	
Units: Percentage of Participants				
number (confidence interval 95%)	33.0 (25.2 to 41.0)	(to)	46.6 (37.5 to 55.2)	

Notes:

[49] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Mono vs Control: Percentage of Participants with PFS at 12 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥20

End point title	Pembro Mono vs Control: Percentage of Participants with PFS at 12 Months per RECIST 1.1 by BICR Among Participants With PD-L1 CPS ≥20

End point description:

PFS is the time from randomization the first documented PD per RECIST 1.1 by BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is ≥20% increase in the SOD of target lesions and an additional absolute increase of ≥5 mm. The appearance of ≥1 new lesions is also PD. Per protocol, PFS in the pembro mono arm versus the control arm as a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS≥20. The percentage of participants with PFS (PFS rate) at 12 months is reported here, for the first course, for all participants in the pembro mono and control arm with CPS≥20. Per protocol, the percentage of participants with PFS at 12 months was compared separately between CPS ≥20 participants of the pembro combo and control arm and is presented earlier.

End point type	Secondary

End point timeframe:

Month 12

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	0[50]	122	
Units: Percentage of Participants				
number (confidence interval 95%)	23.5 (16.6 to 31.1)	(to)	15.1 (9.3 to 22.2)	

Notes:

[50] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Mono vs Control: ORR per RECIST 1.1 by BICR in All Participants

End point title	Pembro Mono vs Control: ORR per RECIST 1.1 by BICR in All Participants

End point description:

ORR was defined as the percentage of participants in the analysis population who have a CR (disappearance of all target lesions) or a PR (≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1. by BICR. Per protocol, ORR in the pembro mono arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment. The percentage of participants who experienced CR or PR is reported here as the ORR, for the first course, for all participants in the pembro mono and control arm. Per protocol, ORR was compared separately between all participants of the pembro combo arm and control arm and is presented earlier.

End point type	Secondary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	301	0[51]	300	
Units: Percentage of Participants				
number (confidence interval 95%)	16.9 (12.9 to 21.7)	(to)	36.0 (30.6 to 41.7)	

Notes:

[51] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	Pembro Mono vs Control: ORR in all subjects

Statistical analysis description:

ORR in all participants of the pembro mono arm was compared to ORR in all participants of the control arm. The comparison was based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 TPS status (Strongly Positive , Not Strongly Positive).

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab +

	Chemotherapy (Control)
Number of subjects included in analysis	601
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1 [52]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in ORR Percentage
Point estimate	-19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.8
upper limit	-12.1

Notes:

[52] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs Control: ORR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1

End point title	Pembro Mono vs Control: ORR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥1

End point description:

ORR was defined as the percentage of participants in the analysis population who have a CR (disappearance of all target lesions) or a PR (≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1. by BICR. Per protocol, ORR in the pembro mono arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥1. The percentage of participants who experienced CR or PR is reported here as the ORR, for the first course, for all participants in the pembro mono and control arm with CPS≥1. Per protocol, ORR was compared separately between CPS ≥1 participants of the pembro combo arm and control arm and is presented earlier.

End point type	Secondary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	257	0[53]	255	
Units: Percentage of Participants				
number (confidence interval 95%)	19.1 (14.5 to 24.4)	(to)	34.9 (29.1 to 41.1)	

Notes:

[53] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	Pembro Mono vs Control: ORR subjects with CPS ≥1

Statistical analysis description:

ORR in CPS ≥1 participants of the pembro mono arm was compared to ORR in CPS ≥1 participants of

the control arm. The comparison was based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 TPS status (Strongly Positive, Not Strongly Positive).

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1 [54]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in ORR Percentage
Point estimate	-15.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.4
upper limit	-8.3

Notes:

[54] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs Control: ORR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥20

End point title	Pembro Mono vs Control: ORR per RECIST 1.1 by BICR in Participants With PD-L1 CPS ≥20

End point description:

ORR was defined as the percentage of participants in the analysis population who have a CR (disappearance of all target lesions) or a PR (≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1. by BICR. Per protocol, ORR in the pembro mono arm versus the control arm was a pre-specified secondary analysis of the ITT population, consisting of all randomized participants during active enrollment with PD-L1 biomarker positive expression defined by IHC as CPS ≥20. The percentage of participants who experienced CR or PR is reported here as the ORR, for the first course, for all participants in the pembro mono and control arm with CPS≥20. Per protocol, ORR was compared separately between CPS ≥20 participants of the pembro combo arm and control arm and is presented earlier.

End point type	Secondary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	0[55]	122	
Units: Percentage of Participants				
number (confidence interval 95%)	23.3 (16.4 to 31.4)	(to)	36.1 (27.6 to 45.3)	

Notes:

[55] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	ORR in participants with CPS≥20

Statistical analysis description:

ORR in CPS ≥20 participants of the pembro mono arm was compared to ORR in CPS ≥20 participants of the control arm. The comparison was based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1) and HPV status (Positive vs. Negative).

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9869 [56]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in ORR Percentage
Point estimate	-12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.8
upper limit	-1.5

Notes:

[56] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs Control: Change From Baseline to Week 15 in the EORTC QLQ-C30 Global Health Status/Quality of Life (Items 29 and 30) Combined Score

End point title	Pembro Mono vs Control: Change From Baseline to Week 15 in the EORTC QLQ-C30 Global Health Status/Quality of Life (Items 29 and 30) Combined Score

End point description:

EORTC-QLQ-C30 is a 30-item questionnaire to assess the quality of life (QoL) of cancer patients. Responses to "How would you rate your overall health during the past week?" (Item 29) and "How would you rate your overall quality of life during the past week?" (Item 30) were scored on a 7-point scale (1=Very Poor to 7=Excellent). Raw scores were standardized by linear transformation so that scores ranged from 0 to 100; a higher score indicating a better overall outcome. Per protocol, change from baseline to Week 15 in GHS/QoL combined score, for the first course, in all participants of the pembro mono versus control arm was a pre-specified secondary analysis; and compared separately between all participants of pembro combo and control arm and is presented earlier. All participants in the pembro mono arm and the control arm who got ≥1 dose of study drug and had assessments available at baseline or post-baseline up to Week 15 were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 15

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	294	0[57]	279	
Units: Score on a Scale				
least squares mean (confidence interval 95%)	0.85 (-1.90 to 3.59)	(to)	0.60 (-2.19 to 3.40)	

Notes:

[57] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	Change from Baseline: EORTC QLQ-C30 Items 29 & 30

Statistical analysis description:

Change from baseline to Week 15 in EORTC-QLQ-C30 GHS/QoL combined score was compared between all participants of the pembro mono arm and the control arm. Comparison based on cLDA model with GHS/QoL score as response variable and treatment by visit interaction, stratification factors (ECOG [0 vs. 1], HPV status [Positive vs. Negative] and PD-L1 TPS status [Strongly Positive, Not Strongly Positive]) as covariates.

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.893 [58]
Method	constrained Longitudinal Data Analysis
Parameter estimate	Difference in LS Means
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.34
upper limit	3.82

Notes:

[58] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs Control: TTD in the EORTC QLQ- H&N35 Pain Score

End point title	Pembro Mono vs Control: TTD in the EORTC QLQ- H&N35 Pain Score

End point description:

EORTC QLQ-H&N35 is a 35-item questionnaire to assess QoL of head and neck cancer patients (7 multi-item scales to assess pain, swallowing, senses, speech, social eating, social contact, sexuality). Responses to the Pain scale (Items 31-34) were scored on a 4-point scale (1=Not at all to 4=Very much). Raw scores were standardized so scores ranged from 0 to 100; a higher score indicating more problems. TTD is the time from BL to first onset of a ≥10-point decrease from BL. Per protocol TTD in Pain Score for first course, in all participants of pembro mono versus control arm was a pre-specified secondary analysis; TTD in pembro combo versus control arm was presented earlier. All participants in the pembro mono and control arm who got ≥1 dose of study drug and completed EORTC QLQ-H&N35 were analyzed. 9999: Value not reached due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

Baseline up to approximately 12 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	295	0[59]	280	
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	(to)	9999 (9999 to 9999)	

Notes:

[59] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	TTD: EORTC QLQ-C30 H&N35 Pain Score

Statistical analysis description:

TTD in EORTC QLQ-H&N35 Pain Score was compared between all participants of the pembro mono arm and the control arm. Comparison based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 TPS status (Strongly Positive, Not Strongly Positive).

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1501 [60]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.21

Notes:

[60] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs Control: TTD in the EORTC QLQ-C30 Global Health Status/Quality of Life (Items 29 and 30) Combined Score

End point title	Pembro Mono vs Control: TTD in the EORTC QLQ-C30 Global Health Status/Quality of Life (Items 29 and 30) Combined Score

End point description:

EORTC-QLQ-C30 is a 30-item questionnaire assessing QoL of cancer patients. Response to "How would you rate your overall health during the past week?" (Item 29) and "How would you rate your overall QoL during the past week?" (Item 30) were scored on a 7-point scale (1=Very Poor to 7=Excellent). Raw scores were standardized so scores ranged from 0 to 100; a higher score indicating a better outcome. TTD is the time from BL to first onset of a ≥10-point decrease from BL in GHS/QoL score. Per protocol TTD for the first course, in all participants of pembro mono versus control arm was a pre-specified secondary analysis; TTD in pembro combo versus control arm was presented earlier. All participants in the pembro mono and control arms who completed EORTC QLQ-C30 and got ≥1 dose of study drug were analyzed. 9999: Value not reached due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

Baseline up to approximately 12 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	294	0[61]	280	
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	(to)	9999 (9999 to 9999)	

Notes:

[61] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	TTD: EORTC QLQ-C30 Items 29 & 30

Statistical analysis description:

TTD in GHS/QoL combined score was compared between all participants of the pembro mono arm and the control arm. Comparison based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 TPS status (Strongly Positive, Not Strongly Positive).

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	574
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.953 [62]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	2

Notes:

[62] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Pembro Mono vs Control: TTD in the EORTC QLQ- H&N35 Swallowing Score

End point title	Pembro Mono vs Control: TTD in the EORTC QLQ- H&N35 Swallowing Score

End point description:

EORTC QLQ-H&N35 is a 35-item questionnaire to assess QoL of head and neck cancer patients (7 multi-item scales to assess pain, swallowing, senses, speech, social eating, social contact, sexuality). Responses to Swallowing scale (Items 35-38) were scored on a 4-point scale (1=Not at all to 4=Very much). Raw scores were standardized so scores ranged from 0 to 100; a higher score indicating more problems. TTD is the time from BL to the first onset of a ≥10-point decrease from BL. Per protocol TTD for the first course, in all participants of the pembro mono versus control arm was a pre-specified secondary analysis; TTD in pembro combo versus control arm was presented earlier. All participants in the pembro mono and control arm who completed the EORTC QLQ-H&N35 and got ≥1 dose of study drug were analyzed. 9999: Value not reached due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

Baseline up to approximately 12 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	295	0[63]	280	
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	(to)	9999 (9999 to 9999)	

Notes:

[63] - Per protocol, the Pembro Combo Arm was not analyzed for this endpoint.

Statistical analyses

Statistical analysis title	TTD: EORTC QLQ-H&N35 Swallowing Score

Statistical analysis description:

TTD in EORTC QLQ-H&N35 Swallowing Score was compared between all participants of the pembro mono arm and the control arm. Comparison based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 TPS status (Strongly Positive, Not Strongly Positive).

Comparison groups	Pembrolizumab Monotherapy (Pembro Mono) v Cetuximab + Chemotherapy (Control)
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8751 [64]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.88

Notes:

[64] - No formal hypothesis testing performed; nominal p-value provided for treatment comparison.

Secondary: Number of Participants Experiencing an Adverse Event (AE)

End point title	Number of Participants Experiencing an Adverse Event (AE)

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor's product was also an AE. The number of participants that experienced at least one AE, for the first course of treatment, in subjects who received

≥1 dose of study drug, was reported for each arm.

End point type	Secondary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	300	276	287	
Units: Participants	290	271	286	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Drug Due to an AE

End point title	Number of Participants Who Discontinued Study Drug Due to an AE

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor’s product was also an AE. The number of participants that experienced at least one AE, for the first course of treatment, in subjects who received ≥1 dose of study drug, was reported for each arm.

End point type	Secondary

End point timeframe:

Up to approximately 47 months

End point values	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Cetuximab + Chemotherapy (Control)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	300	276	287	
Units: Participants	36	90	79	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to approximately 98 months	
Adverse event reporting additional description:	
All Cause Mortality (ACM): all randomized participants. AEs: all randomized participants who got ≥1 dose of study drug. Per protocol, MedDRA preferred terms "Neoplasm progression (NP), Malignant (NP) and Disease progression" not related to study drug are omitted as AEs; ACM and AEs collected and reported separately for pembrolizumab second course.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Pembrolizumab Monotherapy (Pembro Mono)
Reporting group description: -	
Reporting group title	Pembrolizumab + Chemotherapy (Pembro Combo)
Reporting group description: -	
Reporting group title	Pembrolizumab + Chemotherapy Second Course
Reporting group description: -	
Reporting group title	Pembrolizumab Monotherapy Second Course
Reporting group description: -	
Reporting group title	Cetuximab + Chemotherapy (Control)
Reporting group description: -	

Serious adverse events	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Pembrolizumab + Chemotherapy Second Course
Total subjects affected by serious adverse events			
subjects affected / exposed	123 / 300 (41.00%)	165 / 276 (59.78%)	2 / 6 (33.33%)
number of deaths (all causes)	260	242	5
number of deaths resulting from adverse events	25	32	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Cancer pain			
subjects affected / exposed	2 / 300 (0.67%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic tumour necrosis			

subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Hypopharyngeal cancer			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected neoplasm			
subjects affected / exposed	3 / 300 (1.00%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	11 / 300 (3.67%)	6 / 276 (2.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 13	2 / 7	0 / 0
deaths causally related to treatment / all	0 / 2	1 / 2	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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 flare			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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 pain			

subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (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
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Deep vein thrombosis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Circulatory collapse			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurogenic shock			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 300 (0.67%)	4 / 276 (1.45%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			

subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (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
Venous thrombosis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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			
Catheter site inflammation			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Asthenia			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Fatigue			
subjects affected / exposed	3 / 300 (1.00%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 300 (0.67%)	2 / 276 (0.72%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Complication associated with device			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised oedema			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Mucosal inflammation			
subjects affected / exposed	1 / 300 (0.33%)	6 / 276 (2.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 300 (0.67%)	7 / 276 (2.54%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumatosis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Peripheral swelling			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 300 (0.67%)	2 / 276 (0.72%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Sudden death			

subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Swelling face			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Swelling			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Autoinflammatory disease			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Type III immune complex mediated reaction			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Hypersensitivity			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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

Hypoxia			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Hydrothorax			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (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
Epistaxis			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	7 / 300 (2.33%)	2 / 276 (0.72%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 9	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (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
Bronchial obstruction			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Interstitial lung disease			
subjects affected / exposed	1 / 300 (0.33%)	3 / 276 (1.09%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Aspiration			

subjects affected / exposed	2 / 300 (0.67%)	0 / 276 (0.00%)	0 / 6 (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
Pleural effusion			
subjects affected / exposed	2 / 300 (0.67%)	3 / 276 (1.09%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)	2 / 276 (0.72%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Laryngeal oedema			
subjects affected / exposed	1 / 300 (0.33%)	4 / 276 (1.45%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal obstruction			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal fistula			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Pneumonitis			
subjects affected / exposed	3 / 300 (1.00%)	2 / 276 (0.72%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pulmonary artery thrombosis			

subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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 fibrosis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Pulmonary embolism			
subjects affected / exposed	2 / 300 (0.67%)	4 / 276 (1.45%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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 haemorrhage			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper airway obstruction			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Psychiatric disorders			
Stress			

subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Delirium			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Product issues			
Stent malfunction			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Device occlusion			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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 leakage			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Device dislocation			

subjects affected / exposed	0 / 300 (0.00%)	2 / 276 (0.72%)	0 / 6 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
C-reactive protein increased			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Blood potassium decreased			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 300 (0.00%)	3 / 276 (1.09%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood calcium increased			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Neutrophil count decreased			

subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	2 / 300 (0.67%)	1 / 276 (0.36%)	0 / 6 (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
Platelet count decreased			
subjects affected / exposed	0 / 300 (0.00%)	3 / 276 (1.09%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Ankle fracture			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Arterial injury			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (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
Contusion			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Femur fracture			

subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrostomy failure			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Fall			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Osteoradionecrosis			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heat stroke			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Head injury			

subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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 discharge			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Spinal compression fracture			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (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
Stoma site pain			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Traumatic fracture			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheostomy malfunction			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal obstruction			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Tibia fracture			

subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Synovial rupture			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (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
Angina pectoris			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune myocarditis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Cardiac arrest			
subjects affected / exposed	0 / 300 (0.00%)	2 / 276 (0.72%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 300 (0.00%)	2 / 276 (0.72%)	0 / 6 (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
Cardiac failure acute			

subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Supraventricular extrasystoles			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	3 / 300 (1.00%)	3 / 276 (1.09%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Palpitations			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Cardiopulmonary failure			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Tachycardia			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cauda equina syndrome			

subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Cerebral infarction			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Hemiparesis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Carotid artery perforation			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Carotid sinus syndrome			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paralysis			

subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Syncope			
subjects affected / exposed	0 / 300 (0.00%)	2 / 276 (0.72%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Seizure			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (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
Restless legs syndrome			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 300 (0.33%)	14 / 276 (5.07%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	13 / 17	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia of chronic disease			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Febrile neutropenia			
subjects affected / exposed	0 / 300 (0.00%)	17 / 276 (6.16%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	15 / 17	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematotoxicity			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Thrombocytopenia			
subjects affected / exposed	0 / 300 (0.00%)	6 / 276 (2.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Neutropenia			

subjects affected / exposed	0 / 300 (0.00%)	6 / 276 (2.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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 disorders			
Abdominal pain			
subjects affected / exposed	1 / 300 (0.33%)	2 / 276 (0.72%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis microscopic			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Colitis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Abdominal pain upper			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Constipation			
subjects affected / exposed	2 / 300 (0.67%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	2 / 300 (0.67%)	0 / 276 (0.00%)	0 / 6 (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
Duodenal ulcer			

subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Dysphagia			
subjects affected / exposed	4 / 300 (1.33%)	2 / 276 (0.72%)	0 / 6 (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
Enteritis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Diarrhoea			
subjects affected / exposed	2 / 300 (0.67%)	1 / 276 (0.36%)	0 / 6 (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
Gastric ulcer			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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 perforation			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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 haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Haemorrhoids			

subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Haematochezia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Haematemesis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Gastrointestinal toxicity			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Intestinal obstruction			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Intestinal perforation			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Peptic ulcer haemorrhage			

subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Pancreatitis acute			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Oesophageal fistula			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Nausea			
subjects affected / exposed	0 / 300 (0.00%)	6 / 276 (2.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral cavity fistula			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Pneumatosis intestinalis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Pneumoperitoneum			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Stomatitis			
subjects affected / exposed	0 / 300 (0.00%)	8 / 276 (2.90%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	8 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue oedema			

subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Umbilical hernia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Vomiting			
subjects affected / exposed	0 / 300 (0.00%)	5 / 276 (1.81%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	2 / 300 (0.67%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Pruritus			

subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Psoriasis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Skin haemorrhage			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Skin ulcer			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Skin necrosis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Acute kidney injury			
subjects affected / exposed	4 / 300 (1.33%)	5 / 276 (1.81%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 4	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			

subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	1 / 6 (16.67%)
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 failure			
subjects affected / exposed	0 / 300 (0.00%)	3 / 276 (1.09%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular necrosis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Tubulointerstitial nephritis			
subjects affected / exposed	2 / 300 (0.67%)	0 / 276 (0.00%)	0 / 6 (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
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Adrenal insufficiency			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Hypophysitis			

subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Arthralgia			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Joint swelling			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Fistula			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Arthropathy			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Neck pain			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Synovial cyst			

subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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			
Abscess neck			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Abscess limb			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal infection			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Atypical pneumonia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Bacteraemia			

subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 300 (0.67%)	3 / 276 (1.09%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cellulitis			
subjects affected / exposed	2 / 300 (0.67%)	2 / 276 (0.72%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus gastrointestinal infection			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Device related infection			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Device related sepsis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Extradural abscess			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Escherichia infection			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			

subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Gastrointestinal viral infection			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Gastroenteritis norovirus			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Encephalitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Escherichia bacteraemia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Medical device site abscess			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Lower respiratory tract infection			

subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Laryngitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Klebsiella sepsis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Influenza			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Medical device site infection			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Otitis media			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Osteomyelitis			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			

subjects affected / exposed	2 / 300 (0.67%)	0 / 276 (0.00%)	0 / 6 (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
Neutropenic sepsis			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Penile infection			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Pneumonia bacterial			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Pneumonia aspiration			
subjects affected / exposed	5 / 300 (1.67%)	8 / 276 (2.90%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 10	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Pneumonia			
subjects affected / exposed	20 / 300 (6.67%)	23 / 276 (8.33%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 25	7 / 25	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 0
Peritonitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Septic shock			
subjects affected / exposed	1 / 300 (0.33%)	6 / 276 (2.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 1	5 / 5	0 / 0
Sepsis			

subjects affected / exposed	6 / 300 (2.00%)	4 / 276 (1.45%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 300 (0.33%)	4 / 276 (1.45%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelitis			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	1 / 1	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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
Pneumonia staphylococcal			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Pneumonia pseudomonal			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site infection			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (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
Tracheitis			

subjects affected / exposed	1 / 300 (0.33%)	2 / 276 (0.72%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheostomy infection			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	3 / 300 (1.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Skin infection			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	2 / 300 (0.67%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Wound infection			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (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 sepsis			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 300 (0.33%)	5 / 276 (1.81%)	0 / 6 (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
Dehydration			
subjects affected / exposed	1 / 300 (0.33%)	6 / 276 (2.17%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Hyperglycaemia			

subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Hypercalcaemia			
subjects affected / exposed	4 / 300 (1.33%)	3 / 276 (1.09%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Hyperuricaemia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	0 / 6 (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
Hyperkalaemia			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 300 (0.33%)	4 / 276 (1.45%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 300 (0.33%)	7 / 276 (2.54%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	4 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			

subjects affected / exposed	2 / 300 (0.67%)	0 / 276 (0.00%)	0 / 6 (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
Hypomagnesaemia			
subjects affected / exposed	0 / 300 (0.00%)	2 / 276 (0.72%)	0 / 6 (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

Serious adverse events	Pembrolizumab Monotherapy Second Course	Cetuximab + Chemotherapy (Control)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	142 / 287 (49.48%)	
number of deaths (all causes)	5	282	
number of deaths resulting from adverse events	0	28	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic tumour necrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopharyngeal cancer			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected neoplasm			

subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	5 / 287 (1.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 3	
Prostate cancer			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour flare			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurogenic shock			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 8 (0.00%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site inflammation			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Complication associated with device			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoinflammatory disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type III immune complex mediated reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hydrothorax			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemoptysis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal haemorrhage			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal fistula			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumothorax			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 8 (0.00%)	6 / 287 (2.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pulmonary mass			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper airway obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Stress			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			

subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anxiety			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Stent malfunction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device leakage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood calcium increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrostomy failure			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoradionecrosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heat stroke			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site discharge			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy malfunction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial rupture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune myocarditis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cauda equina syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery perforation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid sinus syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 8 (0.00%)	5 / 287 (1.74%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restless legs syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	9 / 287 (3.14%)	
occurrences causally related to treatment / all	0 / 0	10 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of chronic disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	15 / 287 (5.23%)	
occurrences causally related to treatment / all	0 / 0	11 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematotoxicity			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis microscopic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal fistula			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	8 / 287 (2.79%)	
occurrences causally related to treatment / all	0 / 0	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral cavity fistula			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 8 (0.00%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	5 / 287 (1.74%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess neck			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus gastrointestinal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			

subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site abscess			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Penile infection			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	20 / 287 (6.97%)	
occurrences causally related to treatment / all	0 / 0	7 / 24	
deaths causally related to treatment / all	0 / 0	3 / 6	
Peritonitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelitis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stoma site infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tracheitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy infection			

subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular device infection			
subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 8 (0.00%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pembrolizumab Monotherapy (Pembro Mono)	Pembrolizumab + Chemotherapy (Pembro Combo)	Pembrolizumab + Chemotherapy Second Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	265 / 300 (88.33%)	266 / 276 (96.38%)	6 / 6 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 300 (2.00%)	10 / 276 (3.62%)	0 / 6 (0.00%)
occurrences (all)	8	11	0
Hypertension			
subjects affected / exposed	13 / 300 (4.33%)	18 / 276 (6.52%)	0 / 6 (0.00%)
occurrences (all)	14	27	0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	12 / 300 (4.00%)	17 / 276 (6.16%)	0 / 6 (0.00%)
occurrences (all)	12	18	0
Mucosal inflammation			
subjects affected / exposed	12 / 300 (4.00%)	80 / 276 (28.99%)	0 / 6 (0.00%)
occurrences (all)	15	131	0
Malaise			
subjects affected / exposed	6 / 300 (2.00%)	21 / 276 (7.61%)	0 / 6 (0.00%)
occurrences (all)	6	25	0
Fatigue			
subjects affected / exposed	81 / 300 (27.00%)	95 / 276 (34.42%)	1 / 6 (16.67%)
occurrences (all)	94	133	1
Asthenia			
subjects affected / exposed	16 / 300 (5.33%)	46 / 276 (16.67%)	0 / 6 (0.00%)
occurrences (all)	16	75	0
Pyrexia			
subjects affected / exposed	36 / 300 (12.00%)	41 / 276 (14.86%)	0 / 6 (0.00%)
occurrences (all)	41	69	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	2 / 300 (0.67%)	7 / 276 (2.54%)	0 / 6 (0.00%)
occurrences (all)	3	8	0

Rhinitis allergic			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Productive cough			
subjects affected / exposed	17 / 300 (5.67%)	11 / 276 (3.99%)	0 / 6 (0.00%)
occurrences (all)	20	11	0
Oropharyngeal pain			
subjects affected / exposed	9 / 300 (3.00%)	14 / 276 (5.07%)	0 / 6 (0.00%)
occurrences (all)	9	15	0
Increased upper airway secretion			
subjects affected / exposed	3 / 300 (1.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Haemoptysis			
subjects affected / exposed	12 / 300 (4.00%)	11 / 276 (3.99%)	1 / 6 (16.67%)
occurrences (all)	12	14	1
Epistaxis			
subjects affected / exposed	5 / 300 (1.67%)	9 / 276 (3.26%)	0 / 6 (0.00%)
occurrences (all)	6	11	0
Dyspnoea			
subjects affected / exposed	35 / 300 (11.67%)	19 / 276 (6.88%)	0 / 6 (0.00%)
occurrences (all)	43	20	0
Cough			
subjects affected / exposed	40 / 300 (13.33%)	53 / 276 (19.20%)	1 / 6 (16.67%)
occurrences (all)	48	65	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	15 / 300 (5.00%)	12 / 276 (4.35%)	0 / 6 (0.00%)
occurrences (all)	15	13	0
Insomnia			
subjects affected / exposed	21 / 300 (7.00%)	28 / 276 (10.14%)	0 / 6 (0.00%)
occurrences (all)	23	31	0
Investigations			
Blood uric acid increased			
subjects affected / exposed	1 / 300 (0.33%)	2 / 276 (0.72%)	1 / 6 (16.67%)
occurrences (all)	1	4	1
Blood thyroid stimulating hormone increased			

subjects affected / exposed	4 / 300 (1.33%)	6 / 276 (2.17%)	0 / 6 (0.00%)
occurrences (all)	4	6	0
Blood potassium increased			
subjects affected / exposed	0 / 300 (0.00%)	7 / 276 (2.54%)	1 / 6 (16.67%)
occurrences (all)	0	16	1
Blood phosphorus decreased			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Blood creatinine increased			
subjects affected / exposed	12 / 300 (4.00%)	37 / 276 (13.41%)	1 / 6 (16.67%)
occurrences (all)	19	61	1
Aspartate aminotransferase increased			
subjects affected / exposed	17 / 300 (5.67%)	20 / 276 (7.25%)	0 / 6 (0.00%)
occurrences (all)	22	25	0
Alanine aminotransferase increased			
subjects affected / exposed	13 / 300 (4.33%)	19 / 276 (6.88%)	0 / 6 (0.00%)
occurrences (all)	18	23	0
Lymphocyte count decreased			
subjects affected / exposed	10 / 300 (3.33%)	15 / 276 (5.43%)	0 / 6 (0.00%)
occurrences (all)	16	33	0
White blood cell count decreased			
subjects affected / exposed	4 / 300 (1.33%)	36 / 276 (13.04%)	0 / 6 (0.00%)
occurrences (all)	6	76	0
Weight decreased			
subjects affected / exposed	42 / 300 (14.00%)	43 / 276 (15.58%)	1 / 6 (16.67%)
occurrences (all)	43	50	1
Platelet count decreased			
subjects affected / exposed	3 / 300 (1.00%)	53 / 276 (19.20%)	0 / 6 (0.00%)
occurrences (all)	4	98	0
Neutrophil count decreased			
subjects affected / exposed	1 / 300 (0.33%)	50 / 276 (18.12%)	0 / 6 (0.00%)
occurrences (all)	1	85	0
Nervous system disorders			
Dizziness			

subjects affected / exposed	14 / 300 (4.67%)	28 / 276 (10.14%)	0 / 6 (0.00%)
occurrences (all)	16	34	0
Dysgeusia			
subjects affected / exposed	9 / 300 (3.00%)	18 / 276 (6.52%)	0 / 6 (0.00%)
occurrences (all)	9	19	0
Headache			
subjects affected / exposed	36 / 300 (12.00%)	32 / 276 (11.59%)	2 / 6 (33.33%)
occurrences (all)	42	39	2
Neuropathy peripheral			
subjects affected / exposed	1 / 300 (0.33%)	16 / 276 (5.80%)	0 / 6 (0.00%)
occurrences (all)	1	18	0
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 300 (0.67%)	16 / 276 (5.80%)	0 / 6 (0.00%)
occurrences (all)	2	17	0
Presyncope			
subjects affected / exposed	1 / 300 (0.33%)	6 / 276 (2.17%)	1 / 6 (16.67%)
occurrences (all)	1	7	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	61 / 300 (20.33%)	153 / 276 (55.43%)	1 / 6 (16.67%)
occurrences (all)	82	210	1
Neutropenia			
subjects affected / exposed	6 / 300 (2.00%)	90 / 276 (32.61%)	0 / 6 (0.00%)
occurrences (all)	14	135	0
Thrombocytopenia			
subjects affected / exposed	6 / 300 (2.00%)	74 / 276 (26.81%)	0 / 6 (0.00%)
occurrences (all)	6	111	0
Leukopenia			
subjects affected / exposed	4 / 300 (1.33%)	37 / 276 (13.41%)	0 / 6 (0.00%)
occurrences (all)	5	57	0
Lymphopenia			
subjects affected / exposed	7 / 300 (2.33%)	9 / 276 (3.26%)	0 / 6 (0.00%)
occurrences (all)	10	20	0
Ear and labyrinth disorders			
Tinnitus			

subjects affected / exposed	1 / 300 (0.33%)	17 / 276 (6.16%)	0 / 6 (0.00%)
occurrences (all)	1	17	0
Eye disorders			
Vision blurred			
subjects affected / exposed	7 / 300 (2.33%)	5 / 276 (1.81%)	1 / 6 (16.67%)
occurrences (all)	7	5	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 300 (0.67%)	9 / 276 (3.26%)	0 / 6 (0.00%)
occurrences (all)	2	11	0
Gastritis			
subjects affected / exposed	2 / 300 (0.67%)	3 / 276 (1.09%)	1 / 6 (16.67%)
occurrences (all)	2	3	1
Flatulence			
subjects affected / exposed	0 / 300 (0.00%)	3 / 276 (1.09%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Dysphagia			
subjects affected / exposed	20 / 300 (6.67%)	31 / 276 (11.23%)	0 / 6 (0.00%)
occurrences (all)	21	37	0
Dyspepsia			
subjects affected / exposed	10 / 300 (3.33%)	15 / 276 (5.43%)	0 / 6 (0.00%)
occurrences (all)	11	18	0
Dry mouth			
subjects affected / exposed	17 / 300 (5.67%)	20 / 276 (7.25%)	1 / 6 (16.67%)
occurrences (all)	18	23	1
Diarrhoea			
subjects affected / exposed	44 / 300 (14.67%)	77 / 276 (27.90%)	1 / 6 (16.67%)
occurrences (all)	54	121	1
Constipation			
subjects affected / exposed	59 / 300 (19.67%)	101 / 276 (36.59%)	2 / 6 (33.33%)
occurrences (all)	62	145	3
Gastrointestinal pain			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Apical granuloma			

subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	7 / 300 (2.33%)	11 / 276 (3.99%)	0 / 6 (0.00%)
occurrences (all)	7	13	0
Vomiting			
subjects affected / exposed	33 / 300 (11.00%)	90 / 276 (32.61%)	0 / 6 (0.00%)
occurrences (all)	43	155	0
Tongue haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Stomatitis			
subjects affected / exposed	9 / 300 (3.00%)	67 / 276 (24.28%)	0 / 6 (0.00%)
occurrences (all)	9	104	0
Oral pain			
subjects affected / exposed	7 / 300 (2.33%)	18 / 276 (6.52%)	1 / 6 (16.67%)
occurrences (all)	7	18	1
Nausea			
subjects affected / exposed	49 / 300 (16.33%)	140 / 276 (50.72%)	1 / 6 (16.67%)
occurrences (all)	58	271	1
Glossitis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 300 (0.33%)	15 / 276 (5.43%)	0 / 6 (0.00%)
occurrences (all)	1	15	0
Skin fissures			
subjects affected / exposed	0 / 300 (0.00%)	2 / 276 (0.72%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Rash pruritic			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rash maculo-papular			
subjects affected / exposed	9 / 300 (3.00%)	9 / 276 (3.26%)	0 / 6 (0.00%)
occurrences (all)	9	10	0

Rash			
subjects affected / exposed	31 / 300 (10.33%)	30 / 276 (10.87%)	0 / 6 (0.00%)
occurrences (all)	43	37	0
Psoriasis			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 300 (0.67%)	4 / 276 (1.45%)	0 / 6 (0.00%)
occurrences (all)	2	6	0
Dry skin			
subjects affected / exposed	13 / 300 (4.33%)	10 / 276 (3.62%)	1 / 6 (16.67%)
occurrences (all)	16	11	1
Dermatitis acneiform			
subjects affected / exposed	8 / 300 (2.67%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences (all)	9	1	0
Pruritus			
subjects affected / exposed	32 / 300 (10.67%)	24 / 276 (8.70%)	1 / 6 (16.67%)
occurrences (all)	39	26	1
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 276 (0.36%)	1 / 6 (16.67%)
occurrences (all)	0	1	2
Renal failure			
subjects affected / exposed	1 / 300 (0.33%)	5 / 276 (1.81%)	1 / 6 (16.67%)
occurrences (all)	1	6	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	55 / 300 (18.33%)	45 / 276 (16.30%)	1 / 6 (16.67%)
occurrences (all)	57	48	1
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	18 / 300 (6.00%)	28 / 276 (10.14%)	1 / 6 (16.67%)
occurrences (all)	22	30	1
Arthralgia			
subjects affected / exposed	23 / 300 (7.67%)	22 / 276 (7.97%)	1 / 6 (16.67%)
occurrences (all)	29	32	1

Back pain			
subjects affected / exposed	21 / 300 (7.00%)	12 / 276 (4.35%)	0 / 6 (0.00%)
occurrences (all)	22	15	0
Fibromyalgia			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Joint effusion			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	4 / 300 (1.33%)	22 / 276 (7.97%)	0 / 6 (0.00%)
occurrences (all)	4	24	0
Bronchitis			
subjects affected / exposed	5 / 300 (1.67%)	7 / 276 (2.54%)	0 / 6 (0.00%)
occurrences (all)	6	8	0
Paronychia			
subjects affected / exposed	1 / 300 (0.33%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	3 / 300 (1.00%)	2 / 276 (0.72%)	1 / 6 (16.67%)
occurrences (all)	3	2	1
Viral infection			
subjects affected / exposed	0 / 300 (0.00%)	0 / 276 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	15 / 300 (5.00%)	11 / 276 (3.99%)	0 / 6 (0.00%)
occurrences (all)	18	12	0
Tooth infection			
subjects affected / exposed	1 / 300 (0.33%)	1 / 276 (0.36%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Rhinitis			
subjects affected / exposed	2 / 300 (0.67%)	4 / 276 (1.45%)	1 / 6 (16.67%)
occurrences (all)	2	5	1
Pneumonia			

subjects affected / exposed	12 / 300 (4.00%)	19 / 276 (6.88%)	0 / 6 (0.00%)
occurrences (all)	15	22	0
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	10 / 300 (3.33%)	23 / 276 (8.33%)	0 / 6 (0.00%)
occurrences (all)	11	31	0
Hypocalcaemia			
subjects affected / exposed	2 / 300 (0.67%)	17 / 276 (6.16%)	0 / 6 (0.00%)
occurrences (all)	2	23	0
Hyperuricaemia			
subjects affected / exposed	7 / 300 (2.33%)	6 / 276 (2.17%)	0 / 6 (0.00%)
occurrences (all)	9	9	0
Hyperkalaemia			
subjects affected / exposed	8 / 300 (2.67%)	17 / 276 (6.16%)	0 / 6 (0.00%)
occurrences (all)	10	25	0
Hyperglycaemia			
subjects affected / exposed	19 / 300 (6.33%)	15 / 276 (5.43%)	0 / 6 (0.00%)
occurrences (all)	28	23	0
Hypokalaemia			
subjects affected / exposed	23 / 300 (7.67%)	30 / 276 (10.87%)	1 / 6 (16.67%)
occurrences (all)	28	43	1
Dehydration			
subjects affected / exposed	8 / 300 (2.67%)	12 / 276 (4.35%)	0 / 6 (0.00%)
occurrences (all)	8	12	0
Decreased appetite			
subjects affected / exposed	44 / 300 (14.67%)	78 / 276 (28.26%)	0 / 6 (0.00%)
occurrences (all)	51	101	0
Hypercalcaemia			
subjects affected / exposed	12 / 300 (4.00%)	17 / 276 (6.16%)	0 / 6 (0.00%)
occurrences (all)	12	23	0
Hypomagnesaemia			
subjects affected / exposed	12 / 300 (4.00%)	42 / 276 (15.22%)	0 / 6 (0.00%)
occurrences (all)	12	62	0
Hyponatraemia			
subjects affected / exposed	26 / 300 (8.67%)	34 / 276 (12.32%)	0 / 6 (0.00%)
occurrences (all)	31	53	0

Hypophosphataemia			
subjects affected / exposed	8 / 300 (2.67%)	12 / 276 (4.35%)	1 / 6 (16.67%)
occurrences (all)	10	18	4

Non-serious adverse events	Pembrolizumab Monotherapy Second Course	Cetuximab + Chemotherapy (Control)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	278 / 287 (96.86%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 8 (0.00%)	21 / 287 (7.32%)	
occurrences (all)	0	33	
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	16 / 287 (5.57%)	
occurrences (all)	0	19	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	18 / 287 (6.27%)	
occurrences (all)	0	21	
Mucosal inflammation			
subjects affected / exposed	1 / 8 (12.50%)	80 / 287 (27.87%)	
occurrences (all)	1	137	
Malaise			
subjects affected / exposed	1 / 8 (12.50%)	8 / 287 (2.79%)	
occurrences (all)	2	10	
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	101 / 287 (35.19%)	
occurrences (all)	1	162	
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	43 / 287 (14.98%)	
occurrences (all)	0	64	
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	37 / 287 (12.89%)	
occurrences (all)	0	46	
Respiratory, thoracic and mediastinal disorders			

Rhinorrhoea			
subjects affected / exposed	1 / 8 (12.50%)	4 / 287 (1.39%)	
occurrences (all)	1	4	
Rhinitis allergic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	2	
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	6 / 287 (2.09%)	
occurrences (all)	0	6	
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	21 / 287 (7.32%)	
occurrences (all)	0	24	
Increased upper airway secretion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Haemoptysis			
subjects affected / exposed	0 / 8 (0.00%)	8 / 287 (2.79%)	
occurrences (all)	0	10	
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	22 / 287 (7.67%)	
occurrences (all)	0	34	
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	18 / 287 (6.27%)	
occurrences (all)	0	27	
Cough			
subjects affected / exposed	0 / 8 (0.00%)	37 / 287 (12.89%)	
occurrences (all)	0	53	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 8 (0.00%)	15 / 287 (5.23%)	
occurrences (all)	0	18	
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	24 / 287 (8.36%)	
occurrences (all)	1	30	
Investigations			

Blood uric acid increased				
subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)		
occurrences (all)	0	3		
Blood thyroid stimulating hormone increased				
subjects affected / exposed	2 / 8 (25.00%)	7 / 287 (2.44%)		
occurrences (all)	2	10		
Blood potassium increased				
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)		
occurrences (all)	0	3		
Blood phosphorus decreased				
subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)		
occurrences (all)	0	4		
Blood creatinine increased				
subjects affected / exposed	1 / 8 (12.50%)	24 / 287 (8.36%)		
occurrences (all)	1	50		
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 8 (12.50%)	25 / 287 (8.71%)		
occurrences (all)	1	37		
Alanine aminotransferase increased				
subjects affected / exposed	1 / 8 (12.50%)	22 / 287 (7.67%)		
occurrences (all)	1	48		
Lymphocyte count decreased				
subjects affected / exposed	1 / 8 (12.50%)	13 / 287 (4.53%)		
occurrences (all)	2	34		
White blood cell count decreased				
subjects affected / exposed	0 / 8 (0.00%)	46 / 287 (16.03%)		
occurrences (all)	0	110		
Weight decreased				
subjects affected / exposed	0 / 8 (0.00%)	59 / 287 (20.56%)		
occurrences (all)	0	65		
Platelet count decreased				
subjects affected / exposed	0 / 8 (0.00%)	49 / 287 (17.07%)		
occurrences (all)	0	80		
Neutrophil count decreased				

subjects affected / exposed	0 / 8 (0.00%)	55 / 287 (19.16%)	
occurrences (all)	0	106	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	39 / 287 (13.59%)	
occurrences (all)	0	62	
Dysgeusia			
subjects affected / exposed	0 / 8 (0.00%)	16 / 287 (5.57%)	
occurrences (all)	0	19	
Headache			
subjects affected / exposed	0 / 8 (0.00%)	24 / 287 (8.36%)	
occurrences (all)	0	36	
Neuropathy peripheral			
subjects affected / exposed	0 / 8 (0.00%)	8 / 287 (2.79%)	
occurrences (all)	0	10	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 8 (0.00%)	7 / 287 (2.44%)	
occurrences (all)	0	9	
Presyncope			
subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)	
occurrences (all)	0	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 8 (25.00%)	128 / 287 (44.60%)	
occurrences (all)	6	251	
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	93 / 287 (32.40%)	
occurrences (all)	0	194	
Thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	71 / 287 (24.74%)	
occurrences (all)	0	148	
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	41 / 287 (14.29%)	
occurrences (all)	0	87	
Lymphopenia			

subjects affected / exposed	0 / 8 (0.00%)	16 / 287 (5.57%)	
occurrences (all)	0	58	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 8 (0.00%)	19 / 287 (6.62%)	
occurrences (all)	0	21	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 8 (0.00%)	6 / 287 (2.09%)	
occurrences (all)	0	10	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	19 / 287 (6.62%)	
occurrences (all)	0	27	
Gastritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences (all)	0	0	
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	27 / 287 (9.41%)	
occurrences (all)	0	28	
Dyspepsia			
subjects affected / exposed	1 / 8 (12.50%)	24 / 287 (8.36%)	
occurrences (all)	1	28	
Dry mouth			
subjects affected / exposed	0 / 8 (0.00%)	10 / 287 (3.48%)	
occurrences (all)	0	12	
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	96 / 287 (33.45%)	
occurrences (all)	2	191	
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	95 / 287 (33.10%)	
occurrences (all)	0	134	
Gastrointestinal pain			

subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences (all)	0	0	
Apical granuloma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	1 / 8 (12.50%)	19 / 287 (6.62%)	
occurrences (all)	1	24	
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	77 / 287 (26.83%)	
occurrences (all)	0	123	
Tongue haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences (all)	0	0	
Stomatitis			
subjects affected / exposed	0 / 8 (0.00%)	77 / 287 (26.83%)	
occurrences (all)	0	121	
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)	14 / 287 (4.88%)	
occurrences (all)	0	14	
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	146 / 287 (50.87%)	
occurrences (all)	0	273	
Glossitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 8 (0.00%)	15 / 287 (5.23%)	
occurrences (all)	0	15	
Skin fissures			
subjects affected / exposed	0 / 8 (0.00%)	38 / 287 (13.24%)	
occurrences (all)	0	50	
Rash pruritic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	

Rash maculo-papular			
subjects affected / exposed	0 / 8 (0.00%)	16 / 287 (5.57%)	
occurrences (all)	0	24	
Rash			
subjects affected / exposed	2 / 8 (25.00%)	112 / 287 (39.02%)	
occurrences (all)	3	160	
Psoriasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences (all)	0	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 8 (0.00%)	22 / 287 (7.67%)	
occurrences (all)	0	37	
Dry skin			
subjects affected / exposed	0 / 8 (0.00%)	38 / 287 (13.24%)	
occurrences (all)	0	49	
Dermatitis acneiform			
subjects affected / exposed	0 / 8 (0.00%)	84 / 287 (29.27%)	
occurrences (all)	0	130	
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	32 / 287 (11.15%)	
occurrences (all)	0	51	
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Renal failure			
subjects affected / exposed	0 / 8 (0.00%)	2 / 287 (0.70%)	
occurrences (all)	0	2	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 8 (12.50%)	18 / 287 (6.27%)	
occurrences (all)	1	22	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	21 / 287 (7.32%)	
occurrences (all)	0	26	

Arthralgia			
subjects affected / exposed	1 / 8 (12.50%)	18 / 287 (6.27%)	
occurrences (all)	1	20	
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	12 / 287 (4.18%)	
occurrences (all)	0	13	
Fibromyalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 287 (0.00%)	
occurrences (all)	0	0	
Joint effusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	17 / 287 (5.92%)	
occurrences (all)	0	25	
Bronchitis			
subjects affected / exposed	1 / 8 (12.50%)	6 / 287 (2.09%)	
occurrences (all)	1	8	
Paronychia			
subjects affected / exposed	0 / 8 (0.00%)	39 / 287 (13.59%)	
occurrences (all)	0	55	
Pharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	4 / 287 (1.39%)	
occurrences (all)	1	4	
Viral infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	14 / 287 (4.88%)	
occurrences (all)	1	18	
Tooth infection			
subjects affected / exposed	1 / 8 (12.50%)	3 / 287 (1.05%)	
occurrences (all)	1	3	
Rhinitis			

subjects affected / exposed	0 / 8 (0.00%)	3 / 287 (1.05%)	
occurrences (all)	0	4	
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	12 / 287 (4.18%)	
occurrences (all)	0	12	
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	1 / 8 (12.50%)	15 / 287 (5.23%)	
occurrences (all)	4	22	
Hypocalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	22 / 287 (7.67%)	
occurrences (all)	0	49	
Hyperuricaemia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 287 (1.05%)	
occurrences (all)	1	14	
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	18 / 287 (6.27%)	
occurrences (all)	0	49	
Hyperglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	23 / 287 (8.01%)	
occurrences (all)	0	42	
Hypokalaemia			
subjects affected / exposed	0 / 8 (0.00%)	53 / 287 (18.47%)	
occurrences (all)	0	90	
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	16 / 287 (5.57%)	
occurrences (all)	0	20	
Decreased appetite			
subjects affected / exposed	1 / 8 (12.50%)	81 / 287 (28.22%)	
occurrences (all)	1	112	
Hypercalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	8 / 287 (2.79%)	
occurrences (all)	0	9	
Hypomagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	115 / 287 (40.07%)	
occurrences (all)	0	270	

Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	36 / 287 (12.54%)	
occurrences (all)	0	72	
Hypophosphataemia			
subjects affected / exposed	0 / 8 (0.00%)	26 / 287 (9.06%)	
occurrences (all)	0	45	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2015	Amendment 1 included an increase in sample size. The sample size increased from 750 to 780 based on prevalence of strongly positive PD-L1 expression seen in data from the HNSCC cohorts in other MK-3475 Pembrolizumab studies. Added PFS hypothesis for pembrolizumab in combination with chemotherapy vs. standard treatment in subjects with strongly positive PD-L1 expression.
06 September 2015	Amendment 5 included changes to OS. OS was changed from a secondary objective to a primary objective, and biomarker population was updated to include PD-L1 ≥20% CPS, ≥10% CPS, ≥1% CPS. Sample size increased from 780 to 825 due to these changes. The strongly positive PD-L1 enrichment population was removed. Added QOL secondary objectives. Changed ORR, DOR, and PFS per irRECIST from secondary to exploratory objectives. Modified inclusion and exclusion criteria.
06 April 2017	Amendment 7 included references to PD-L1 10% Combined Positive Score were removed; only the 20% and 1% cut points are planned to be analyzed.
13 September 2017	Amendment 8 included follow-up time was increased at the interim and final analyses by 3 months to achieve data maturity at these timepoints.
27 November 2017	Amendment 9 included dose modification guidelines were updated per health authority feedback. Hypotheses for PFS and OS superiority in biomarker positive subpopulation were added. Follow-up time was increased at the second interim analysis and final analysis to allow adequate follow-up time to assess long-term effects of pembrolizumab. Language was added to enable survival follow-up activities throughout the study at timepoints specified by the Sponsor.
30 January 2019	Amendment 10 modified to indicate the number of expected events, rather than required events, references to “event-driven” were removed, and text was modified to describe the timing of the final analysis to account for the scenario if the number of deaths for one hypothesis accumulates slower than expected to prevent the trial continuing for an unreasonable period for the final analysis.
21 April 2020	Amendment 11 corrected the typographical error "co-primary" that appears at the end of the second paragraph in Section 4.2.3.1.1 has been corrected to "dual-primary" to indicate that the 2 primary endpoints in the study, OS and PFS, were "dual-primary" endpoints rather than "co-primary" endpoints. As a result, the study is considered positive if a statistically significant result is determined for either of these endpoints. This error has appeared in all versions of the protocol starting with amendment 048-05, dated 05-AUG-2016.
10 June 2021	Amendment 12 updated the pembrolizumab dose modification table and toxicity management guidelines for irAEs, in line with FDA request to harmonize the presentation of safety information across all FDA-approved PD-1/L-1 antibody prescribing information. To align with the updated SmPC for cetuximab.
21 July 2022	Amendment 13 added language to allow subjects to roll over to a pembrolizumab extension study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported