Clinical trial results:
A Phase III Randomized Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel, Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer

Summary

EudraCT number	2014-002009-40
Trial protocol	BE IE IT DE ES HU AT NL SE DK GB PT FR PL
Global end of trial date	01 October 2020

Results information

Result version number	v1 (current)
This version publication date	07 October 2021
First version publication date	07 October 2021

Trial information

Trial identification

Sponsor protocol code	3475-045

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02256436
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-3475-045

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., 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	01 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2016
Global end of trial reached?	Yes
Global end of trial date	01 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Participants with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy will be randomly assigned to receive Investigator's choice of paclitaxel, docetaxel, or vinflunine (Control), or pembrolizumab. The primary study hypotheses are that pembrolizumab will prolong Overall Survival (OS) and Progression-free Survival (PFS) compared to paclitaxel, docetaxel, or vinflunine.

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	22 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	Denmark: 19
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Israel: 40
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Japan: 52
Country: Number of subjects enrolled	Korea, Republic of: 31
Country: Number of subjects enrolled	Netherlands: 29
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Peru: 2

Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Taiwan: 23
Country: Number of subjects enrolled	Turkey: 13
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 106
Worldwide total number of subjects	542
EEA total number of subjects	219

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)	230
From 65 to 84 years	306
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

13 participants randomized to receive Control switched over to receive Pembrolizumab. Per protocol, response/progression or adverse events that occurred during a non-randomized switch-over or second course of pembrolizumab were not counted towards efficacy or safety outcome measures, respectively. These results are for randomized treatment only.

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	Control

Arm description:

Participants received paclitaxel 175 mg/m^2 intravenously (IV) or docetaxel 75 mg/m^2 IV or vinflunine 320 mg/m^2 IV, on Day 1 of each 3-week cycle (Q3W). Eligible participants who experienced disease progression may have been able to switch over to receive pembrolizumab 200 mg IV Q3W for up to 35 treatment administrations (up to approximately 2 years).

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

Dosage and administration details:

175 mg/m^2 IV on Day 1 Q3W

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

Dosage and administration details:

75 mg/m^2 IV on Day 1 Q3W

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

Dosage and administration details:

320 mg/m^2 IV on Day 1 Q3W

Arm title	Pembrolizumab

Arm description:

Participants received pembrolizumab 200 mg IV on Day 1 Q3W. Eligible participants who stopped pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab 200 mg IV Q3W for up to 17 cycles (up to approximately 1 additional year).

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

Dosage and administration details:

200 mg IV on Day 1 Q3W.

Number of subjects in period 1	Control	Pembrolizumab
Started	272	270
Treated	255	266
Switched Over to Pembrolizumab	13	0
Completed	0	0
Not completed	272	270
Adverse event, serious fatal	216	208
Physician decision	1	-
Consent withdrawn by subject	26	10
Adverse event, non-fatal	9	14
Transferred to Extension Study	11	23
Lost to follow-up	1	2
Did Not Continue on Extension Study	8	12
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
Participants received paclitaxel 175 mg/m^2 intravenously (IV) or docetaxel 75 mg/m^2 IV or vinflunine 320 mg/m^2 IV, on Day 1 of each 3-week cycle (Q3W). Eligible participants who experienced disease progression may have been able to switch over to receive pembrolizumab 200 mg IV Q3W for up to 35 treatment administrations (up to approximately 2 years).	
Reporting group title	Pembrolizumab
Reporting group description:	
Participants received pembrolizumab 200 mg IV on Day 1 Q3W. Eligible participants who stopped pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab 200 mg IV Q3W for up to 17 cycles (up to approximately 1 additional year).	

Reporting group values	Control	Pembrolizumab	Total
Number of subjects	272	270	542
Age categorical Units: Subjects			
Adults (18-64 years)	125	105	230
Elderly (From 65-84 years)	147	159	306
Elderly 85 years and over	0	6	6
Age Continuous Units: Years			
arithmetic mean	65.1	66.0	
standard deviation	± 9.2	± 10.2	-
Sex: Female, Male Units:			
Female	70	70	140
Male	202	200	402

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Participants received paclitaxel 175 mg/m^2 intravenously (IV) or docetaxel 75 mg/m^2 IV or vinflunine 320 mg/m^2 IV, on Day 1 of each 3-week cycle (Q3W). Eligible participants who experienced disease progression may have been able to switch over to receive pembrolizumab 200 mg IV Q3W for up to 35 treatment administrations (up to approximately 2 years).	
Reporting group title	Pembrolizumab
Reporting group description:	
Participants received pembrolizumab 200 mg IV on Day 1 Q3W. Eligible participants who stopped pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab 200 mg IV Q3W for up to 17 cycles (up to approximately 1 additional year).	

Primary: Progression-Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) - All Participants

End point title	Progression-Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) - All Participants
End point description:	
PFS was defined as the time from randomization to the first documented disease progression, or death due to any cause, whichever occurred first. Per RECIST 1.1, progressive disease (PD) was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered PD. The PFS per RECIST 1.1 was assessed by blinded independent central review (BICR) in all participants up through the primary analysis database cut-off date of 07-Sep-2016. The analysis population consisted of all randomized participants, regardless of whether or not they received study treatment. Participants were included in the treatment group to which they were randomized.	
End point type	Primary
End point timeframe:	
Through primary analysis database cut-off date of 07-Sep-2016 (Up to approximately 20 months)	

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	270		
Units: Months				
median (confidence interval 95%)	3.3 (2.3 to 3.5)	2.1 (2.0 to 2.2)		

Statistical analyses

Statistical analysis title	PFS - All Participants
Comparison groups	Pembrolizumab v Control

Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.41648 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.19

Notes:

[1] - One-sided p-value based on stratified log-rank test

Primary: Overall Survival (OS) - All Participants

End point title	Overall Survival (OS) - All Participants

End point description:

OS was defined as the time from randomization to death due to any cause. The OS was assessed in all participants up through the primary analysis database cut-off date of 07-Sep-2016. The analysis population consisted of all randomized participants, regardless of whether or not they received study treatment. Participants were included in the treatment group to which they were randomized.

End point type	Primary

End point timeframe:

Through primary analysis database cut-off date of 07-Sep-2016 (Up to approximately 20 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	270		
Units: Months				
median (confidence interval 95%)	7.4 (6.1 to 8.3)	10.3 (8.0 to 11.8)		

Statistical analyses

Statistical analysis title	OS - All Participants
Comparison groups	Pembrolizumab v Control
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00224 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.91

Notes:

[2] - One-sided p-value based on stratified log-rank test

Primary: PFS per RECIST 1.1 - Participants with Programmed Cell Death-Ligand (PD-L1) Positive Tumors

End point title	PFS per RECIST 1.1 - Participants with Programmed Cell Death-Ligand (PD-L1) Positive Tumors

End point description:

PFS was defined as the time from randomization to the first documented disease progression, or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered PD. PFS per RECIST 1.1 was assessed by BICR in all participants who had PD-L1 positive tumors (combined positive score [CPS] ≥1%) up through the primary analysis database cut-off date of 07-Sep-2016. The analysis population consisted of all randomized PD-L1 positive participants, regardless of whether or not they received study treatment. Participants were included in the treatment group to which they were randomized.

End point type	Primary

End point timeframe:

Through primary analysis database cut-off date of 07-Sep-2016 (Up to approximately 20 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	110		
Units: Months				
median (confidence interval 95%)	3.2 (2.2 to 3.4)	2.1 (2.0 to 2.4)		

Statistical analyses

Statistical analysis title	PFS - PD-L1 positive participants
Comparison groups	Pembrolizumab v Control
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.26443 [3]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.24

Notes:

[3] - One-sided p-value based on stratified log-rank test

Primary: OS - Participants with PD-L1 Positive Tumors

End point title	OS - Participants with PD-L1 Positive Tumors

End point description:

OS was defined as the time from randomization to death due to any cause. For the purposes of this study, participants with PD-L1 CPS ≥1% were considered to have a PD-L1 positive tumor status. OS was assessed in all participants who had PD-L1 positive tumors (CPS ≥1%) up through the primary analysis database cut-off date of 07-Sep-2016. The analysis population consisted of all randomized PD-L1 positive participants, regardless of whether or not they received study treatment. Participants were included in the treatment group to which they were randomized.

End point type	Primary

End point timeframe:

Through primary analysis database cut-off date of 07-Sep-2016 (Up to approximately 20 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	110		
Units: Months				
median (confidence interval 95%)	6.9 (4.7 to 8.8)	11.3 (7.7 to 16.0)		

Statistical analyses

Statistical analysis title	OS - PD-L1 positive participants
Comparison groups	Pembrolizumab v Control
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00239 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.86

Notes:

[4] - One-sided p-value based on stratified log-rank test

Primary: PFS per RECIST 1.1 - Participants with Strongly PD-L1 Positive Tumors

End point title	PFS per RECIST 1.1 - Participants with Strongly PD-L1 Positive Tumors

End point description:

PFS was defined as the time from randomization to the first documented disease progression, or death

due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered PD. PFS per RECIST 1.1 was assessed by BICR in all participants who had strongly PD-L1 positive tumors (CPS ≥10%) up through the primary analysis database cut-off date of 07-Sep-2016. The analysis population consisted of all randomized strongly PD-L1 positive participants, regardless of whether or not they received study treatment. Participants were included in the treatment group to which they were randomized.

End point type	Primary

End point timeframe:

Through primary analysis database cut-off date of 07-Sep-2016 (Up to approximately 20 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	74		
Units: Months				
median (confidence interval 95%)	3.1 (2.2 to 3.4)	2.1 (1.9 to 2.1)		

Statistical analyses

Statistical analysis title	PFS - Strongly PD-L1 positive participants
Comparison groups	Pembrolizumab v Control
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.23958 [5]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.28

Notes:

[5] - One-sided p-value based on stratified log-rank test

Primary: OS - Participants with Strongly PD-L1 Positive Tumors

End point title	OS - Participants with Strongly PD-L1 Positive Tumors

End point description:

OS was defined as the time from randomization to death due to any cause. For the purposes of this study, participants with a PD-L1 CPS ≥10% were considered to have a strongly PD-L1 positive tumor status. The OS was assessed in all participants who had strongly PD-L1 positive tumors (CPS ≥10%) up through the primary analysis database cut-off date of 07-Sep-2016. The analysis population consisted of all randomized strongly PD-L1 positive participants, regardless of whether or not they received study treatment. Participants were included in the treatment group to which they were randomized.

End point type	Primary

End point timeframe:

Through primary analysis database cut-off date of 07-Sep-2016 (Up to approximately 20 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	74		
Units: Months				
median (confidence interval 95%)	5.2 (4.0 to 7.4)	8.0 (5.0 to 12.3)		

Statistical analyses

Statistical analysis title	OS - Strongly PD-L1 positive participants
Comparison groups	Pembrolizumab v Control
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00483 [6]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.88

Notes:

[6] - One-sided p-value based on stratified log-rank test

Secondary: Number of Participants Who Experienced an Adverse Event (AE)

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

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. Participants were monitored for the occurrence of nonserious AEs for up to 30 days after last dose of study treatment and for serious AEs for up to 90 days after last dose of study treatment. The number of participants who experienced an AE was reported for each arm. The analysis population consisted of all randomized participants who received at least one dose of study treatment. Participants were included in the treatment group corresponding to the study treatment they actually received.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	266		
Units: Participants	250	250		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants Who Discontinued Study Treatment 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. Participants were monitored for the occurrence of nonserious AEs for up to 30 days after last dose of study treatment and for serious AEs for up to 90 days after last dose of study treatment. The number of participants who discontinued study treatment due to an AE was reported for each arm. The analysis population consisted of all randomized participants who received at least one dose of study treatment. Participants were included in the treatment group corresponding to the study treatment they actually received.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	266		
Units: Participants	36	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) per RECIST 1.1 - Participants with Strongly PD-L1 Positive Tumors

End point title	Objective Response Rate (ORR) per RECIST 1.1 - Participants with Strongly PD-L1 Positive Tumors

End point description:

ORR was defined as the percentage of participants in the analysis population who had a Complete Response (CR: disappearance of all target lesions) or a Partial Response (PR: at least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1. ORR was assessed by BICR in participants with strongly PD-L1 positive tumors (CPS ≥10%) up through the final analysis database cut-off date of 26-Oct-2017. The analysis population consisted of all randomized strongly PD-L1 positive participants, regardless of whether or not they received study treatment. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	74		
Units: Percentage of Participants				
number (confidence interval 95%)	6.7 (2.5 to 13.9)	20.3 (11.8 to 31.2)		

Statistical analyses

Statistical analysis title	ORR per RECIST 1.1 - Strongly PD-L1 Positive Pts
Comparison groups	Control v Pembrolizumab
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00061 [7]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in Percentages
Point estimate	17.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.8
upper limit	29.4

Notes:

[7] - One-sided p-value for testing
H0: difference in %=0; H1: difference in %>0

Secondary: ORR per RECIST 1.1 - Participants with PD-L1 Positive Tumors

End point title	ORR per RECIST 1.1 - Participants with PD-L1 Positive Tumors

End point description:

ORR was defined as the percentage of participants in the analysis population who had a CR (disappearance of all target lesions) or a PR (at least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1. ORR was assessed by BICR in participants with PD-L1 positive tumors (CPS ≥1%) up through the final analysis database cut-off date of 26-Oct-2017. The analysis population consisted of all randomized PD-L1 positive participants, regardless of whether or not they received study treatment. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	110		
Units: Percentage of Participants				
number (confidence interval 95%)	8.3 (4.1 to 14.8)	22.7 (15.3 to 31.7)		

Statistical analyses

Statistical analysis title	ORR per RECIST 1.1 - PD-L1 Positive Participants
Comparison groups	Control v Pembrolizumab
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00049 [8]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in Percentages
Point estimate	15.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.5
upper limit	25.7

Notes:

[8] - One-sided p-value for testing
H0: difference in %=0; H1: difference in %>0

Secondary: ORR Per RECIST 1.1 - All Participants

End point title	ORR Per RECIST 1.1 - All Participants

End point description:

ORR was defined as the percentage of participants in the analysis population who had a CR (disappearance of all target lesions) or a PR (at least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1. ORR was assessed by BICR in all participants up through the final analysis database cut-off date of 26-Oct-2017. The analysis population consisted of all randomized participants, regardless of whether or not they received study treatment. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	270		
Units: Percentage of Participants				
number (confidence interval 95%)	11.0 (7.6 to 15.4)	21.1 (16.4 to 26.5)		

Statistical analyses

Statistical analysis title	ORR per RECIST 1.1 - All Participants
Comparison groups	Control v Pembrolizumab
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00068 [9]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in Percentages
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	16.2

Notes:

[9] - One-sided p-value for testing
H0: difference in %=0; H1: difference in %>0

Secondary: PFS per Modified RECIST (mRECIST) - Participants with Strongly PD-L1 Positive Tumors

End point title	PFS per Modified RECIST (mRECIST) - Participants with Strongly PD-L1 Positive Tumors

End point description:

PFS was defined as the time from randomization to the first documented disease progression, or death due to any cause, whichever occurred first. Per mRECIST, PD was defined as at least 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered PD. Per mRECIST, confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented was required for participants remaining on treatment following PD per RECIST 1.1. PFS per mRECIST was assessed by BICR in participants with strongly PD-L1 positive tumors (CPS ≥10%) up through the final analysis database cut-off date of 26-Oct-2017. All randomized strongly PD-L1 positive participants [Pts] were analysed, according to the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	74		
Units: Months				
median (confidence interval 95%)	3.3 (2.4 to 3.7)	2.1 (2.0 to 3.7)		

Statistical analyses

Statistical analysis title	PFS per mRECIST - Strongly PD-L1 Positive Pts
Comparison groups	Control v Pembrolizumab
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.07066 [10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.11

Notes:

[10] - One-sided p-value based on stratified log-rank test

Secondary: PFS per mRECIST - Participants with PD-L1 Positive Tumors

End point title	PFS per mRECIST - Participants with PD-L1 Positive Tumors

End point description:

PFS was defined as the time from randomization to the first documented disease progression, or death due to any cause, whichever occurred first. Per mRECIST, PD was defined as at least 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered PD. Per mRECIST, confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented was required for participants remaining on treatment following PD per RECIST 1.1. PFS per mRECIST was assessed by BICR in participants with PD-L1 positive tumors (CPS ≥1%) up through the final analysis database cut-off date of 26-Oct-2017. All randomized PD-L1 positive participants were analysed, according to the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	110		
Units: Months				
median (confidence interval 95%)	3.3 (2.6 to 3.6)	2.1 (2.0 to 3.7)		

Statistical analyses

Statistical analysis title	PFS per mRECIST - PD-L1 Positive Participants
Comparison groups	Control v Pembrolizumab
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.08745 [11]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.1

Notes:

[11] - One-sided p-value based on stratified log-rank test

Secondary: PFS per mRECIST - All Participants

End point title	PFS per mRECIST - All Participants

End point description:

PFS was defined as the time from randomization to the first documented disease progression, or death due to any cause, whichever occurred first. Per mRECIST, PD was defined as at least 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered PD. Per mRECIST, confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented was required for participants remaining on treatment following PD per RECIST 1.1. PFS per mRECIST was assessed by BICR in all randomized participants up through the final analysis database cut-off date of 26-Oct-2017. All randomized participants were analysed, according to the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	270		
Units: Months				
median (confidence interval 95%)	3.4 (3.1 to 3.8)	2.2 (2.1 to 3.3)		

Statistical analyses

Statistical analysis title	PFS per mRECIST - All Participants
Comparison groups	Control v Pembrolizumab

Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.05328 [12]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.04

Notes:

[12] - One-sided p-value based on stratified log-rank test

Secondary: ORR per mRECIST - Participants with Strongly PD-L1 Positive Tumors

End point title	ORR per mRECIST - Participants with Strongly PD-L1 Positive Tumors

End point description:

ORR per mRECIST was defined as the percentage of participants in the analysis population who had a CR (complete disappearance of all lesions (and no new lesions), with confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented) or a PR (decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation). ORR per mRECIST was assessed by BICR in participants with strongly PD-L1 positive tumors (CPS ≥10%) up through the final analysis database cut-off date of 26-Oct-2017. The analysis population consisted of all randomized strongly PD-L1 positive participants, regardless of whether or not they received study treatment. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	74		
Units: Percentage of Participants				
number (confidence interval 95%)	7.8 (3.2 to 15.4)	24.3 (15.1 to 35.7)		

Statistical analyses

Statistical analysis title	ORR per mRECIST - Strongly PD-L1 Positive Pts
Comparison groups	Control v Pembrolizumab

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00009 [13]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in Percentages
Point estimate	21.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.1
upper limit	34.2

Notes:

[13] - One-sided p-value for testing
H0: difference in %=0; H1: difference in %>0

Secondary: ORR per mRECIST - Participants with PD-L1 Positive Tumors

End point title	ORR per mRECIST - Participants with PD-L1 Positive Tumors

End point description:

ORR per mRECIST was defined as the percentage of participants in the analysis population who had a CR (complete disappearance of all lesions (and no new lesions), with confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented) or a PR (decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation). ORR per mRECIST was assessed by BICR in participants with PD-L1 positive tumors (CPS ≥1%) up through the final analysis database cut-off date of 26-Oct-2017. The analysis population consisted of all randomized PD-L1 positive participants, regardless of whether or not they received study treatment. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	110		
Units: Percentage of Participants				
number (confidence interval 95%)	9.2 (4.7 to 15.8)	28.2 (20.0 to 37.6)		

Statistical analyses

Statistical analysis title	ORR per mRECIST - PD-L1 Positive Participants
Comparison groups	Control v Pembrolizumab

Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00002 [14]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in Percentages
Point estimate	21
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.1
upper limit	31.5

Notes:

[14] - One-sided p-value for testing
H0: difference in %=0; H1: difference in %>0

Secondary: ORR per mRECIST - All Participants

End point title	ORR per mRECIST - All Participants

End point description:

ORR per mRECIST was defined as the percentage of participants in the analysis population who had a CR (complete disappearance of all lesions (and no new lesions), with confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented) or a PR (decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation). ORR per mRECIST was assessed by BICR in all participants up through the final analysis database cut-off date of 26-Oct-2017. The analysis population consisted of all randomized participants, regardless of whether or not they received study treatment. Participants were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	270		
Units: Percentage of Participants				
number (confidence interval 95%)	11.4 (7.9 to 15.8)	25.2 (20.1 to 30.8)		

Statistical analyses

Statistical analysis title	ORR per mRECIST - All Participants
Comparison groups	Control v Pembrolizumab
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00001 [15]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in Percentages
Point estimate	13.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	7.4
upper limit	20.3

Notes:

[15] - One-sided p-value for testing
H0: difference in %=0; H1: difference in %>0

Secondary: Duration of Response (DOR) per RECIST 1.1 - Participants with Strongly PD-L1 Positive Tumors

End point title	Duration of Response (DOR) per RECIST 1.1 - Participants with Strongly PD-L1 Positive Tumors

End point description:

DOR was defined as the time from first documented evidence of CR or PR until disease progression or death. Per protocol, the DOR for participants who had progressed or died at the time of analysis, who had started a new anti-cancer treatment, who were lost to follow-up, or who had an ongoing response was to be censored at the date of their last tumor assessment. DOR was analysed in all randomized participants who had strongly PD-L1 positive tumors (CPS ≥10%) and who demonstrated a confirmed CR or PR per RECIST 1.1 based on BICR using the Kaplan-Meier method. Values of 8888 indicate the DOR upper 95% confidence limit was undefined because the DOR rate was not low enough at the time of the cut-off date. Values of 9999 indicate the median DOR was not reached because there were not enough events and the DOR upper 95% confidence limit was undefined because the DOR rate was not low enough at the time of the cut-off date.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	15		
Units: Months				
median (confidence interval 95%)	4.4 (2.8 to 8888)	9999 (8.2 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR per RECIST 1.1 - Participants with PD-L1 Positive Tumors

End point title	DOR per RECIST 1.1 - Participants with PD-L1 Positive Tumors

End point description:

DOR was defined as the time from first documented evidence of CR or PR until disease progression or death. Per protocol, the DOR for participants who had progressed or died at the time of analysis, who had started a new anti-cancer treatment, who were lost to follow-up, or who had an ongoing response was to be censored at the date of their last tumor assessment. DOR was analysed in all randomized participants who had PD-L1 positive tumors (CPS ≥1%) and who demonstrated a confirmed CR or PR per RECIST 1.1 based on BICR using the Kaplan-Meier method. Values of 9999 indicate the median DOR was not reached because there were not enough events and the DOR upper 95% confidence limit was undefined because the DOR rate was not low enough at the time of the cut-off date.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	25		
Units: Months				
median (confidence interval 95%)	9999 (2.8 to 9999)	9999 (21.8 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR per RECIST 1.1 - All Participants

End point title	DOR per RECIST 1.1 - All Participants

End point description:

DOR was defined as the time from first documented evidence of CR or PR until disease progression or death. Per protocol, the DOR for participants who had progressed or died at the time of analysis, who had started a new anti-cancer treatment, who were lost to follow-up, or who had an ongoing response was to be censored at the date of their last tumor assessment. DOR was analysed in all randomized participants who demonstrated a confirmed CR or PR per RECIST 1.1 based on BICR using the Kaplan-Meier method. Values of 9999 indicate the median DOR was not reached because there were not enough events and the DOR upper 95% confidence limit was undefined because the DOR rate was not low enough at the time of the cut-off date.

End point type	Secondary

End point timeframe:

Through final analysis database cut-off date of 26-Oct-2017 (Up to approximately 34 months)

End point values	Control	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	57		
Units: Months				
median (confidence interval 95%)	4.4 (4.0 to 20.3)	9999 (15.9 to 9999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Through end of trial analysis database cut-off date of 01-Oct-2020 (Up to approximately 71 months)

Adverse event reporting additional description:

AEs include all treated participants according to treatment received. MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" unrelated to drug excluded as AEs. 13 participants randomized to receive Control were switched over to pembrolizumab per protocol and monitored for AEs separately.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Control

Reporting group description:

Participants received paclitaxel 175 mg/m^2 IV or docetaxel 75 mg/m^2 IV or vinflunine 320 mg/m^2 IV, on Day 1 of each 3-week cycle (Q3W). Eligible participants who experienced disease progression may have been able to switch over to receive pembrolizumab 200 mg IV Q3W for up to 35 treatment administrations (up to approximately 2 years).

Reporting group title	Control Switched Over to Pembrolizumab

Reporting group description:

Per protocol, participants originally randomized to the Control arm that experienced disease progression were switched over to receive pembrolizumab 200 mg IV on Day 1 Q3W.

Reporting group title	Pembrolizumab

Reporting group description:

Participants receive pembrolizumab 200 mg IV on Day 1 Q3W. Eligible participants who stopped pembrolizumab with SD or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab 200 mg IV Q3W for up to 17 cycles (up to approximately 1 additional year).

Serious adverse events	Control	Control Switched Over to Pembrolizumab	Pembrolizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	104 / 255 (40.78%)	8 / 13 (61.54%)	107 / 266 (40.23%)
number of deaths (all causes)	230	9	224
number of deaths resulting from adverse events	4	0	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	3 / 255 (1.18%)	0 / 13 (0.00%)	2 / 266 (0.75%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			

subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Lung neoplasm malignant			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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 central nervous system			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Prostate cancer recurrent			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Tumour pain			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Urethral cancer			

subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	2 / 266 (0.75%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Hypertension			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Hypovolaemic shock			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac artery occlusion			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			

subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasoconstriction			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	0 / 255 (0.00%)	1 / 13 (7.69%)	0 / 266 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Death			
subjects affected / exposed	5 / 255 (1.96%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	1 / 5	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 5	0 / 0	1 / 1
Fatigue			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	2 / 266 (0.75%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	3 / 266 (1.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hyperthermia malignant			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Influenza like illness			

subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Mucosal inflammation			
subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	5 / 255 (1.96%)	2 / 13 (15.38%)	5 / 266 (1.88%)
occurrences causally related to treatment / all	1 / 6	1 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fluid collection			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Pelvic pain			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	2 / 266 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	3 / 266 (1.13%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Interstitial lung disease			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	3 / 266 (1.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 255 (0.00%)	1 / 13 (7.69%)	6 / 266 (2.26%)
occurrences causally related to treatment / all	0 / 0	1 / 1	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pulmonary embolism			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Product issues			

Device dislocation			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	3 / 266 (1.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device malfunction			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	0 / 255 (0.00%)	1 / 13 (7.69%)	0 / 266 (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 / 255 (0.00%)	1 / 13 (7.69%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 255 (0.00%)	1 / 13 (7.69%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial test positive			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood calcium increased			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	0 / 266 (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

Lipase increased			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	0 / 266 (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
Platelet count decreased			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Transaminases increased			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Incisional hernia			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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

Pelvic fracture			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site haemorrhage			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Atrial fibrillation			

subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	0 / 266 (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
Atrial flutter			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Myocardial infarction			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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 haemorrhage			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral infarction			

subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Encephalopathy			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Somnolence			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Syncope			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 255 (2.75%)	0 / 13 (0.00%)	6 / 266 (2.26%)
occurrences causally related to treatment / all	6 / 8	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia of malignant disease			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	16 / 255 (6.27%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	16 / 16	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	4 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrogenic anaemia			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Neutropenia			
subjects affected / exposed	5 / 255 (1.96%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normocytic anaemia			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Pancytopenia			
subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	0 / 266 (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
Thrombocytopenia			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 255 (1.57%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal incontinence			

subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Colitis			
subjects affected / exposed	0 / 255 (0.00%)	1 / 13 (7.69%)	5 / 266 (1.88%)
occurrences causally related to treatment / all	0 / 0	2 / 2	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	7 / 255 (2.75%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	7 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	3 / 266 (1.13%)
occurrences causally related to treatment / all	1 / 2	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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 perforation			

subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ileus			
subjects affected / exposed	3 / 255 (1.18%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	8 / 255 (3.14%)	2 / 13 (15.38%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	5 / 8	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal pseudo-obstruction			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Large intestinal obstruction			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Nausea			
subjects affected / exposed	1 / 255 (0.39%)	1 / 13 (7.69%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic colitis			

subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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	1 / 255 (0.39%)	1 / 13 (7.69%)	0 / 266 (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
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			

subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 255 (2.35%)	0 / 13 (0.00%)	5 / 266 (1.88%)
occurrences causally related to treatment / all	2 / 6	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune nephritis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Azotaemia			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Bladder neck obstruction			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	4 / 255 (1.57%)	0 / 13 (0.00%)	6 / 266 (2.26%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			

subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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 failure			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	2 / 266 (0.75%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal injury			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Urinary tract obstruction			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	3 / 266 (1.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia of malignancy			

subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	2 / 266 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Hypophysitis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Gouty arthritis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	2 / 266 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendonitis			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Periostitis			

subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bacteraemia			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	2 / 266 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Cystitis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			

subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 255 (0.00%)	1 / 13 (7.69%)	0 / 266 (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
Epididymitis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fournier's gangrene			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Gastroenteritis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	2 / 266 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic infection			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii infection			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	8 / 255 (3.14%)	1 / 13 (7.69%)	11 / 266 (4.14%)
occurrences causally related to treatment / all	1 / 9	0 / 1	2 / 11
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Post procedural infection			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Psoas abscess			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Sepsis			
subjects affected / exposed	5 / 255 (1.96%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences causally related to treatment / all	2 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	12 / 255 (4.71%)	0 / 13 (0.00%)	12 / 266 (4.51%)
occurrences causally related to treatment / all	4 / 13	0 / 0	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	5 / 266 (1.88%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular device infection			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	2 / 266 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Decreased appetite			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Dehydration			
subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	3 / 266 (1.13%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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			
subjects affected / exposed	2 / 255 (0.78%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 255 (0.39%)	0 / 13 (0.00%)	0 / 266 (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
Vitamin B1 deficiency			
subjects affected / exposed	0 / 255 (0.00%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Control	Control Switched Over to Pembrolizumab	Pembrolizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	237 / 255 (92.94%)	11 / 13 (84.62%)	236 / 266 (88.72%)
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 255 (3.14%)	1 / 13 (7.69%)	14 / 266 (5.26%)
occurrences (all)	8	1	19
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	52 / 255 (20.39%)	0 / 13 (0.00%)	33 / 266 (12.41%)
occurrences (all)	67	0	36
Fatigue			
subjects affected / exposed	85 / 255 (33.33%)	3 / 13 (23.08%)	66 / 266 (24.81%)
occurrences (all)	107	3	83
Influenza like illness			

subjects affected / exposed	7 / 255 (2.75%)	1 / 13 (7.69%)	10 / 266 (3.76%)
occurrences (all)	8	2	14
Mucosal inflammation			
subjects affected / exposed	18 / 255 (7.06%)	0 / 13 (0.00%)	6 / 266 (2.26%)
occurrences (all)	24	0	8
Oedema peripheral			
subjects affected / exposed	39 / 255 (15.29%)	0 / 13 (0.00%)	31 / 266 (11.65%)
occurrences (all)	48	0	36
Pyrexia			
subjects affected / exposed	30 / 255 (11.76%)	1 / 13 (7.69%)	36 / 266 (13.53%)
occurrences (all)	38	1	44
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	18 / 255 (7.06%)	3 / 13 (23.08%)	39 / 266 (14.66%)
occurrences (all)	20	3	51
Dyspnoea exertional			
subjects affected / exposed	9 / 255 (3.53%)	1 / 13 (7.69%)	5 / 266 (1.88%)
occurrences (all)	11	1	5
Dyspnoea			
subjects affected / exposed	23 / 255 (9.02%)	0 / 13 (0.00%)	31 / 266 (11.65%)
occurrences (all)	23	0	38
Productive cough			
subjects affected / exposed	5 / 255 (1.96%)	1 / 13 (7.69%)	8 / 266 (3.01%)
occurrences (all)	5	1	12
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 255 (0.78%)	1 / 13 (7.69%)	5 / 266 (1.88%)
occurrences (all)	2	1	6
Delirium			
subjects affected / exposed	4 / 255 (1.57%)	1 / 13 (7.69%)	3 / 266 (1.13%)
occurrences (all)	5	1	3
Insomnia			
subjects affected / exposed	20 / 255 (7.84%)	2 / 13 (15.38%)	19 / 266 (7.14%)
occurrences (all)	20	2	22
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	4 / 255 (1.57%)	0 / 13 (0.00%)	14 / 266 (5.26%)
occurrences (all)	5	0	15
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 255 (1.18%)	0 / 13 (0.00%)	14 / 266 (5.26%)
occurrences (all)	4	0	15
Blood alkaline phosphatase increased			
subjects affected / exposed	8 / 255 (3.14%)	1 / 13 (7.69%)	9 / 266 (3.38%)
occurrences (all)	8	1	9
Blood bilirubin increased			
subjects affected / exposed	2 / 255 (0.78%)	1 / 13 (7.69%)	4 / 266 (1.50%)
occurrences (all)	2	1	4
Blood creatinine increased			
subjects affected / exposed	13 / 255 (5.10%)	2 / 13 (15.38%)	13 / 266 (4.89%)
occurrences (all)	16	2	22
Neutrophil count decreased			
subjects affected / exposed	40 / 255 (15.69%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences (all)	73	0	1
Platelet count decreased			
subjects affected / exposed	8 / 255 (3.14%)	1 / 13 (7.69%)	4 / 266 (1.50%)
occurrences (all)	11	1	4
Weight decreased			
subjects affected / exposed	22 / 255 (8.63%)	1 / 13 (7.69%)	25 / 266 (9.40%)
occurrences (all)	23	1	30
White blood cell count decreased			
subjects affected / exposed	22 / 255 (8.63%)	0 / 13 (0.00%)	1 / 266 (0.38%)
occurrences (all)	41	0	1
Injury, poisoning and procedural complications			
Procedural pneumothorax			
subjects affected / exposed	0 / 255 (0.00%)	1 / 13 (7.69%)	0 / 266 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 255 (7.45%)	0 / 13 (0.00%)	19 / 266 (7.14%)
occurrences (all)	26	0	22
Dysgeusia			

subjects affected / exposed	14 / 255 (5.49%)	0 / 13 (0.00%)	7 / 266 (2.63%)
occurrences (all)	16	0	7
Headache			
subjects affected / exposed	14 / 255 (5.49%)	2 / 13 (15.38%)	14 / 266 (5.26%)
occurrences (all)	18	2	19
Neuropathy peripheral			
subjects affected / exposed	31 / 255 (12.16%)	0 / 13 (0.00%)	3 / 266 (1.13%)
occurrences (all)	43	0	3
Peripheral sensory neuropathy			
subjects affected / exposed	28 / 255 (10.98%)	0 / 13 (0.00%)	2 / 266 (0.75%)
occurrences (all)	34	0	3
Paraesthesia			
subjects affected / exposed	4 / 255 (1.57%)	1 / 13 (7.69%)	6 / 266 (2.26%)
occurrences (all)	4	1	9
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	86 / 255 (33.73%)	1 / 13 (7.69%)	45 / 266 (16.92%)
occurrences (all)	139	1	61
Neutropenia			
subjects affected / exposed	41 / 255 (16.08%)	0 / 13 (0.00%)	0 / 266 (0.00%)
occurrences (all)	74	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 255 (0.00%)	1 / 13 (7.69%)	5 / 266 (1.88%)
occurrences (all)	0	1	5
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	33 / 255 (12.94%)	1 / 13 (7.69%)	32 / 266 (12.03%)
occurrences (all)	40	1	37
Abdominal pain upper			
subjects affected / exposed	14 / 255 (5.49%)	0 / 13 (0.00%)	9 / 266 (3.38%)
occurrences (all)	16	0	11
Constipation			
subjects affected / exposed	79 / 255 (30.98%)	2 / 13 (15.38%)	54 / 266 (20.30%)
occurrences (all)	105	2	63
Diarrhoea			

subjects affected / exposed	47 / 255 (18.43%)	1 / 13 (7.69%)	43 / 266 (16.17%)
occurrences (all)	69	2	72
Nausea			
subjects affected / exposed	73 / 255 (28.63%)	2 / 13 (15.38%)	56 / 266 (21.05%)
occurrences (all)	100	2	62
Stomatitis			
subjects affected / exposed	23 / 255 (9.02%)	0 / 13 (0.00%)	7 / 266 (2.63%)
occurrences (all)	35	0	8
Vomiting			
subjects affected / exposed	34 / 255 (13.33%)	0 / 13 (0.00%)	38 / 266 (14.29%)
occurrences (all)	47	0	47
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	100 / 255 (39.22%)	0 / 13 (0.00%)	2 / 266 (0.75%)
occurrences (all)	106	0	2
Dermatitis acneiform			
subjects affected / exposed	3 / 255 (1.18%)	1 / 13 (7.69%)	4 / 266 (1.50%)
occurrences (all)	3	1	4
Dermatitis allergic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 13 (7.69%)	0 / 266 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	9 / 255 (3.53%)	1 / 13 (7.69%)	17 / 266 (6.39%)
occurrences (all)	9	1	19
Pruritus			
subjects affected / exposed	15 / 255 (5.88%)	0 / 13 (0.00%)	66 / 266 (24.81%)
occurrences (all)	17	0	88
Rash			
subjects affected / exposed	18 / 255 (7.06%)	1 / 13 (7.69%)	32 / 266 (12.03%)
occurrences (all)	19	1	40
Rash maculo-papular			
subjects affected / exposed	3 / 255 (1.18%)	1 / 13 (7.69%)	7 / 266 (2.63%)
occurrences (all)	5	1	8
Urticaria			
subjects affected / exposed	5 / 255 (1.96%)	1 / 13 (7.69%)	6 / 266 (2.26%)
occurrences (all)	5	1	6

Renal and urinary disorders			
Haematuria			
subjects affected / exposed	17 / 255 (6.67%)	1 / 13 (7.69%)	30 / 266 (11.28%)
occurrences (all)	21	1	43
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 255 (0.00%)	1 / 13 (7.69%)	11 / 266 (4.14%)
occurrences (all)	0	1	11
Hypothyroidism			
subjects affected / exposed	3 / 255 (1.18%)	1 / 13 (7.69%)	21 / 266 (7.89%)
occurrences (all)	3	1	24
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	31 / 255 (12.16%)	1 / 13 (7.69%)	30 / 266 (11.28%)
occurrences (all)	57	1	35
Musculoskeletal pain			
subjects affected / exposed	9 / 255 (3.53%)	1 / 13 (7.69%)	15 / 266 (5.64%)
occurrences (all)	10	1	16
Back pain			
subjects affected / exposed	21 / 255 (8.24%)	2 / 13 (15.38%)	40 / 266 (15.04%)
occurrences (all)	22	2	47
Myalgia			
subjects affected / exposed	17 / 255 (6.67%)	1 / 13 (7.69%)	17 / 266 (6.39%)
occurrences (all)	24	1	20
Pain in extremity			
subjects affected / exposed	27 / 255 (10.59%)	0 / 13 (0.00%)	24 / 266 (9.02%)
occurrences (all)	31	0	28
Synovitis			
subjects affected / exposed	0 / 255 (0.00%)	1 / 13 (7.69%)	0 / 266 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 255 (1.57%)	1 / 13 (7.69%)	15 / 266 (5.64%)
occurrences (all)	4	1	23
Pharyngitis			

subjects affected / exposed	1 / 255 (0.39%)	1 / 13 (7.69%)	1 / 266 (0.38%)
occurrences (all)	1	2	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 255 (0.78%)	1 / 13 (7.69%)	10 / 266 (3.76%)
occurrences (all)	2	1	12
Urinary tract infection			
subjects affected / exposed	27 / 255 (10.59%)	2 / 13 (15.38%)	33 / 266 (12.41%)
occurrences (all)	30	2	45
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	53 / 255 (20.78%)	4 / 13 (30.77%)	57 / 266 (21.43%)
occurrences (all)	65	4	64
Hypoalbuminaemia			
subjects affected / exposed	9 / 255 (3.53%)	1 / 13 (7.69%)	9 / 266 (3.38%)
occurrences (all)	9	1	10
Hypomagnesaemia			
subjects affected / exposed	4 / 255 (1.57%)	1 / 13 (7.69%)	5 / 266 (1.88%)
occurrences (all)	5	2	6
Hyponatraemia			
subjects affected / exposed	18 / 255 (7.06%)	0 / 13 (0.00%)	16 / 266 (6.02%)
occurrences (all)	21	0	20
Hypophosphataemia			
subjects affected / exposed	8 / 255 (3.14%)	1 / 13 (7.69%)	5 / 266 (1.88%)
occurrences (all)	16	2	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 October 2014	The primary changes of amendment 2 (AM2) included the addition of docetaxel as a comparator to the Control arm and changes to study eligibility.
19 November 2015	The primary changes of AM4 included elevating PFS and OS in participants with PD-L1 positive and PD-L1 strongly positive tumors to co-primary objectives.
15 March 2016	The primary changes of AM9 included elevating PFS and OS in participants with PD-L1 positive and PD-L1 strongly positive tumors to co-primary objectives.
19 June 2016	The primary changes of AM11 included allowing the second interim analysis and/or the final analysis to be postponed to accrue additional OS events in PD-L1 positive participants after the planned number of OS events in all participants was achieved.
27 September 2016	The primary changes of AM13 included clarifying the basis for PD-L1 positive and strongly positive categories using CPS cut-points determined from other pembrolizumab studies.
21 December 2016	The primary changes of AM15 included adding a Crossover phase to the study to allow eligible participants in the Control arm who experienced PD to crossover to pembrolizumab 200 mg Q3W.
22 November 2017	The primary changes of AM17 included changes to dose modification language, addition of study extension language, and clarifying the approved dose of pembrolizumab.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported