Clinical trial results:
A phase II single arm clinical trial of nivolumab (BMS-936558) in subjects with metastatic or unresectable urothelial cancer who have progressed or recurred following treatment with a platinum agent

Summary

EudraCT number	2014-003625-17
Trial protocol	DE ES BE SE CZ FI PL IT
Global end of trial date	12 November 2021

Results information

Result version number	v1 (current)
This version publication date	27 October 2022
First version publication date	27 October 2022

Trial information

Trial identification

Sponsor protocol code	CA209-275

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate ORR based on blinded independent review committee (BIRC) assessments (using RECIST 1.1) of nivolumab monotherapy in subjects with tumor expressing PD-L1 and overall treated subjects with metastatic or surgically unresectable urothelial cancer who have progressed or recurred following treatment with a platinum agent.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Japan: 23
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United States: 106
Worldwide total number of subjects	270
EEA total number of subjects	135

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)	122
From 65 to 84 years	145
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

270 participants were treated.

Period 1

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

Arms

Arm title	Nivolumab 3 mg/kg

Arm description:

Nivolumab 3 mg/kg was administered as a 60 minute IV infusion Q2W

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

Dosage and administration details:

Nivolumab 3 mg/kg

Number of subjects in period 1	Nivolumab 3 mg/kg
Started	270
Completed	0
Not completed	270
Adverse event, serious fatal	1
Poor/Non-Compliance	1
Subject Withdrew Consent	5
Other Reasons	5
Participant Request to Discontinue Treatment	20
Adverse Event Unrelated to Study Drug	39
Study Drug Toxicity	31
Lost to follow-up	1
Disease Progression	167

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab 3 mg/kg
Reporting group description:	
Nivolumab 3 mg/kg was administered as a 60 minute IV infusion Q2W	

Reporting group values	Nivolumab 3 mg/kg	Total	
Number of subjects	270	270	
Age categorical Units: Subjects			
Adults (18-64 years)	122	122	
From 65-84 years	145	145	
85 years and over	3	3	
Age Continuous Units: Years			
arithmetic mean	65.0		
standard deviation	± 9.38	-	
Sex: Female, Male Units:			
Female	59	59	
Male	211	211	
Race/Ethnicity, Customized Units: Subjects			
Asian	30	30	
White	231	231	
Black or African American	2	2	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Other	3	3	
Not Reported	4	4	
Ethnicity (NIH/OMB) Units: Subjects			
Not Hispanic or Latino	156	156	
Hispanic or Latino	2	2	
Unknown or Not Reported	112	112	

End points

End points reporting groups

Reporting group title	Nivolumab 3 mg/kg

Reporting group description:

Nivolumab 3 mg/kg was administered as a 60 minute IV infusion Q2W

Primary: Objective Response Rate per BIRC Assessment

End point title	Objective Response Rate per BIRC Assessment[1]

End point description:

Objective Response Rate (ORR) was defined as the number of participants with a best overall response of confirmed Complete Response (CR) or Partial Response (PR) (per RECIST 1.1 criteria) divided by the number of all treated participants. RECIST 1.1 = Response Evaluation Criteria in Solid Tumors. CR= Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR= At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. BIRC= blinded independent review committee

End point type	Primary

End point timeframe:

From the date of first dose to the date of objectively documented progression or the date of subsequent therapy, whichever occurs first (assessed up to 14 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics were planned for this endpoint

End point values	Nivolumab 3 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	265			
Units: Percent of participants				
number (confidence interval 95%)	19.6 (15.0 to 24.9)			

Statistical analyses

No statistical analyses for this end point

Primary: ORR per BIRC Assessment by PD-L1 expression level

End point title	ORR per BIRC Assessment by PD-L1 expression level[2]

End point description:

Objective Response Rate (ORR) was defined as the number of participants with a best overall response of confirmed Complete Response (CR) or Partial Response (PR) (per RECIST 1.1 criteria) divided by the number of all treated participants. RECIST 1.1 = Response Evaluation Criteria in Solid Tumors. CR= Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR= At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. BIRC= blinded independent review committee PD-L1 expression level= membranous staining in greater than or equal to 5% and greater than or equal to 1% tumor cells. n = Number of participants in each category

End point type	Primary

End point timeframe:

From the date of first dose to the date of objectively documented progression or the date of subsequent therapy, whichever occurs first (assessed up to 14 months)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics were planned for this endpoint

End point values	Nivolumab 3 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	265			
Units: Percent of Participants				
number (confidence interval 95%)				
PD-L1 <1%	16.1 (10.5 to 23.1)			
PD-L1 >= 1%	23.8 (16.5 to 32.3)			
PD-L1 <5%	15.8 (10.8 to 21.8)			
PD-L1 >=5%	28.4 (18.9 to 39.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Duration of Response (DOR)

End point title	Duration of Response (DOR)[3]

End point description:

DOR is defined as the time from first confirmed response, complete response (CR) or partial response (PR) to the date of the first documented tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first. Participants who start subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessments prior to initiation of the subsequent anticancer therapy. Participants who die without a reported prior progression will be considered to have progressed on the date of their death. Participants who neither progress nor die will be censored on the date of their last evaluable tumor assessment.

"99999"=N/A

End point type	Primary

End point timeframe:

From the first confirmed response to the date of the first documented tumor progression or death due to any cause, whichever occurs first (up to approximately 14 months)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics were planned for this endpoint

End point values	Nivolumab 3 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Months				
median (confidence interval 95%)	99999 (7.43 to 99999)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Response (TTR)

End point title	Time to Response (TTR)[4]

End point description:

TTR is defined as the time from first dosing date to the date of the first confirmed complete response (CR) or partial response (PR), as assessed by the Blinded Independent Review Committee (BIRC). Complete response is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. Partial response is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Primary

End point timeframe:

From first dosing date to the date of the first confirmed response (up to approximately 14 months)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics were planned for this endpoint

End point values	Nivolumab 3 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Months				
median (full range (min-max))	1.87 (1.6 to 5.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) per Investigator

End point title	Objective Response Rate (ORR) per Investigator

End point description:

Investigator-assessed ORR was defined as the percent of participants with a best overall response of confirmed complete response (CR) or partial response (PR). Complete response is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. Partial response is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. PD-L1 expression level = Membranous staining in greater than or equal to 5% and greater than or equal to 1% tumor cells.

End point type	Secondary

End point timeframe:

From the date of first dose to the date of objectively documented progression or the date of subsequent therapy, whichever occurs first (up to approximately 45 months)

End point values	Nivolumab 3 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	270			
Units: Percent of Participants				
number (confidence interval 95%)				
All treated participants	24.8 (19.8 to 30.4)			
PD-L1 <1%	19.9 (13.7 to 27.3)			
PD-L1 >= 1%	30.6 (22.7 to 39.6)			
PD-L1 <5%	20.9 (15.3 to 27.4)			
PD-L1 >=5%	33.7 (23.7 to 44.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival was defined as the time from first dosing date to the date of death. A participant who had not died was censored at last known date alive. PD-L1 expression level = membranous staining in greater than or equal to 5% and greater than or equal to 1% tumor cells.

End point type	Secondary

End point timeframe:

From first dosing date to the date of death (up to approximately 23 months)

End point values	Nivolumab 3 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	270			
Units: Months				
median (confidence interval 95%)				
All treated participants	8.57 (6.05 to 11.27)			
PD-L1 <1%	5.95 (4.37 to 8.08)			
PD-L1 >= 1%	11.86 (9.10 to 19.12)			
PD-L1 <5%	6.24 (4.96 to 9.00)			
PD-L1 >=5%	13.54 (9.63 to 22.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time from first dosing date to the date of the first documented tumor progression, based on Blinded Independent Review Committee (BIRC) assessments or death due to any cause. Progression was defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions. PD-L1 expression level is defined as membranous staining in greater than or equal to 5% and greater than or equal to 1% tumor cells.

End point type	Secondary

End point timeframe:

From first dosing date to the date of the first documented tumor progression (up to approximately 6 months)

End point values	Nivolumab 3 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	270			
Units: Months				
median (confidence interval 95%)				
All treated participants	1.94 (1.87 to 2.33)			
PD-L1 <1%	1.87 (1.74 to 2.00)			
PD-L1 >= 1%	3.45 (1.91 to 3.71)			
PD-L1 <5%	1.87 (1.81 to 2.04)			
PD-L1 >=5%	3.68 (1.91 to 5.52)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Duration of Response (DOR) - Extended Collection

End point title	Duration of Response (DOR) - Extended Collection

End point description:

DOR is the time from first confirmed response, complete (CR) or partial response (PR) to the date of the first tumor progression PER RECIST 1.1 criteria or death due to any cause, whichever occurs first.

Participants without prior reported progression will be censored at the last evaluable tumor assessments prior to subsequent anticancer therapy. Participants who die without a reported prior progression will be considered on the date of their death. Participants who neither progress nor die will be censored on the date of their last evaluable tumor assessment. CR is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR is defined as at least a 30% decrease in the sum of diameters of target lesions. Note: This outcome measure represents an updated version of the primary endpoint to include additional data collection that has occurred after the primary completion date.

End point type	Post-hoc

End point timeframe:

From the first confirmed response to the date of the first documented tumor progression or death due to any cause, whichever occurs first (up to approximately 32 months)

End point values	Nivolumab 3 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Months				
median (confidence interval 95%)	20.27 (11.50 to 31.31)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Time to Response (TTR) - Extended Collection

End point title	Time to Response (TTR) - Extended Collection

End point description:

TTR is defined as the time from first dosing date to the date of the first confirmed complete response (CR) or partial response (PR), as assessed by the Blinded Independent Review Committee (BIRC). Complete response is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. Partial response is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Note: This outcome measure represents an updated version of the primary endpoint to include additional data collection that has occurred after the primary completion date.

End point type	Post-hoc

End point timeframe:

From first dosing date to the date of the first confirmed response (up to approximately 14 months)

End point values	Nivolumab 3 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Months				
median (full range (min-max))	1.97 (1.6 to 13.8)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Objective Response Rate (ORR) per BIRC Assessment - Extended Collection

End point title	Objective Response Rate (ORR) per BIRC Assessment - Extended Collection

End point description:

Objective Response Rate (ORR) was defined as the percent of participants with a best overall response of confirmed Complete Response (CR) or Partial Response (PR) (per RECIST 1.1 criteria). RECIST 1.1 = Response Evaluation Criteria in Solid Tumors. CR= Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR= At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. BIRC= blinded independent review committee PD-L1 expression level= membranous staining in greater than or equal to 5% and greater than or equal to 1% tumor cells.

Note: This outcome measure represents an updated version of the primary endpoint to include additional data collection that has occurred after the primary completion date."

End point type	Post-hoc

End point timeframe:

From the date of first dose to the date of objectively documented progression or the date of subsequent therapy, whichever occurs first (up approximately to 43 months)

End point values	Nivolumab 3 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	270			
Units: Percent of Participants				
number (confidence interval 95%)				
All treated participants	20.7 (16.1 to 26.1)			
PD-L1 <1%	16.4 (10.8 to 23.5)			
PD-L1 >= 1%	25.8 (18.4 to 34.4)			
PD-L1 <5%	16.0 (11.1 to 22.1)			
PD-L1 >=5%	31.3 (21.6 to 42.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants were assessed for all-cause mortality from their first dose to study completion, (up to approximately 80 months).

SAEs and NSAEs were assessed from first dose to 100 days following last dose (up to approximately 78 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Nivolumab 3 mg/kg

Reporting group description:

Nivolumab 3 mg/kg was administered as a 60 minute IV infusion Q2W

Serious adverse events	Nivolumab 3 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	199 / 270 (73.70%)		
number of deaths (all causes)	225		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	4 / 270 (1.48%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	95 / 270 (35.19%)		
occurrences causally related to treatment / all	0 / 100		
deaths causally related to treatment / all	0 / 89		
Metastases to bone			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			

subjects affected / exposed	4 / 270 (1.48%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Metastases to lung				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Transitional cell cancer of renal pelvis and ureter metastatic				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Transitional cell carcinoma				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Tumour associated fever				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Adenocarcinoma pancreas				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transitional cell carcinoma recurrent				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bladder neoplasm				

subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Arteriovenous fistula				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Circulatory collapse				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Hypertension				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	4 / 270 (1.48%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Shock haemorrhagic				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Superior vena cava syndrome				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arteriosclerosis				

subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hypotension				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Obstruction				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
General physical health deterioration				
subjects affected / exposed	12 / 270 (4.44%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 10			
Fatigue				
subjects affected / exposed	3 / 270 (1.11%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				

subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	4 / 270 (1.48%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	5 / 270 (1.85%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Malaise				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Mass				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic mass				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sudden death				

subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Systemic inflammatory response syndrome				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	5 / 270 (1.85%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Interstitial lung disease				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	3 / 270 (1.11%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	7 / 270 (2.59%)			
occurrences causally related to treatment / all	8 / 8			
deaths causally related to treatment / all	1 / 1			
Pleural effusion				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				

subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	4 / 270 (1.48%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	1 / 2		
Haemoptysis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis in device			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood bilirubin increased			
subjects affected / exposed	3 / 270 (1.11%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 1		

Lipase increased			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Quality of life decreased			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver function test increased			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Influenza A virus test positive			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infusion related reaction				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	3 / 270 (1.11%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardio-respiratory arrest				

subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pericarditis				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiovascular disorder				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic valve stenosis				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypertensive heart disease				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Brain oedema				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebellar haematoma				

subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral disorder				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Monoplegia				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Paraesthesia				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				

subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 270 (1.11%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 270 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Agranulocytosis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Uveitis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 270 (1.48%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		

Colitis				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Duodenitis				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	7 / 270 (2.59%)			
occurrences causally related to treatment / all	5 / 9			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	4 / 270 (1.48%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				

subjects affected / exposed	3 / 270 (1.11%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Nausea				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	4 / 270 (1.48%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 1			
Small intestinal obstruction				
subjects affected / exposed	7 / 270 (2.59%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 3			
Rectal haemorrhage				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Autoimmune colitis				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer haemorrhage				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastritis				

subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Immune-mediated enterocolitis				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic failure				
subjects affected / exposed	3 / 270 (1.11%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Biliary obstruction				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				

subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Pemphigoid			
subjects affected / exposed	2 / 270 (0.74%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Rash pruritic			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	2 / 270 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	4 / 270 (1.48%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	3 / 270 (1.11%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Bladder tamponade			
subjects affected / exposed	2 / 270 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
subjects affected / exposed	2 / 270 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal impairment			

subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal failure			
subjects affected / exposed	2 / 270 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	3 / 270 (1.11%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Hypophysitis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 270 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Synovitis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Arthritis infective			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Bronchitis			
subjects affected / exposed	2 / 270 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Candida infection			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	6 / 270 (2.22%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Stoma site cellulitis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			

subjects affected / exposed	4 / 270 (1.48%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	1 / 1			
Sepsis				
subjects affected / exposed	12 / 270 (4.44%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 4			
Urinary tract infection				
subjects affected / exposed	17 / 270 (6.30%)			
occurrences causally related to treatment / all	0 / 18			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	3 / 270 (1.11%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Anal abscess				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial infection				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchiolitis				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Endocarditis				

subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronavirus infection				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Kidney infection				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infected lymphocele				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 270 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	2 / 270 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				

subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	2 / 270 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	2 / 270 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Hyperkalaemia			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypervolaemia			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 270 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Nivolumab 3 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	245 / 270 (90.74%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	17 / 270 (6.30%)		
occurrences (all)	17		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	43 / 270 (15.93%)		
occurrences (all)	50		
Pyrexia			
subjects affected / exposed	65 / 270 (24.07%)		
occurrences (all)	85		
Oedema peripheral			
subjects affected / exposed	45 / 270 (16.67%)		
occurrences (all)	53		
Fatigue			
subjects affected / exposed	97 / 270 (35.93%)		
occurrences (all)	115		
Chills			
subjects affected / exposed	22 / 270 (8.15%)		
occurrences (all)	26		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	59 / 270 (21.85%)		
occurrences (all)	75		
Dyspnoea			
subjects affected / exposed	45 / 270 (16.67%)		
occurrences (all)	53		
Pneumonitis			
subjects affected / exposed	15 / 270 (5.56%)		
occurrences (all)	18		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	17 / 270 (6.30%)		
occurrences (all)	18		
Insomnia			
subjects affected / exposed	29 / 270 (10.74%)		
occurrences (all)	30		
Investigations			
Blood creatinine increased			
subjects affected / exposed	24 / 270 (8.89%)		
occurrences (all)	31		
Weight decreased			
subjects affected / exposed	24 / 270 (8.89%)		
occurrences (all)	25		
Amylase increased			
subjects affected / exposed	20 / 270 (7.41%)		
occurrences (all)	35		
Lipase increased			
subjects affected / exposed	18 / 270 (6.67%)		
occurrences (all)	37		
Blood alkaline phosphatase increased			
subjects affected / exposed	14 / 270 (5.19%)		
occurrences (all)	15		
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 270 (7.41%)		
occurrences (all)	59		
Dizziness			
subjects affected / exposed	21 / 270 (7.78%)		
occurrences (all)	27		
Paraesthesia			
subjects affected / exposed	14 / 270 (5.19%)		
occurrences (all)	14		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	58 / 270 (21.48%)		
occurrences (all)	72		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	60 / 270 (22.22%) 111		
Constipation subjects affected / exposed occurrences (all)	60 / 270 (22.22%) 74		
Abdominal pain subjects affected / exposed occurrences (all)	34 / 270 (12.59%) 39		
Vomiting subjects affected / exposed occurrences (all)	42 / 270 (15.56%) 54		
Nausea subjects affected / exposed occurrences (all)	71 / 270 (26.30%) 93		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	45 / 270 (16.67%) 69		
Rash subjects affected / exposed occurrences (all)	46 / 270 (17.04%) 60		
Dry skin subjects affected / exposed occurrences (all)	16 / 270 (5.93%) 16		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	22 / 270 (8.15%) 31		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	32 / 270 (11.85%) 32		
Musculoskeletal and connective tissue disorders Pain in extremity			

subjects affected / exposed occurrences (all)	25 / 270 (9.26%) 27		
Myalgia subjects affected / exposed occurrences (all)	20 / 270 (7.41%) 23		
Back pain subjects affected / exposed occurrences (all)	41 / 270 (15.19%) 48		
Arthralgia subjects affected / exposed occurrences (all)	40 / 270 (14.81%) 52		
Bone pain subjects affected / exposed occurrences (all)	14 / 270 (5.19%) 14		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	43 / 270 (15.93%) 63		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	20 / 270 (7.41%) 29		
Nasopharyngitis subjects affected / exposed occurrences (all)	16 / 270 (5.93%) 20		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	74 / 270 (27.41%) 78		
Dehydration subjects affected / exposed occurrences (all)	21 / 270 (7.78%) 25		
Hypokalaemia subjects affected / exposed occurrences (all)	15 / 270 (5.56%) 16		
Hyperglycaemia			

subjects affected / exposed	16 / 270 (5.93%)		
occurrences (all)	24		
Hyponatraemia			
subjects affected / exposed	19 / 270 (7.04%)		
occurrences (all)	22		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2014	Added amylase and lipase; Changed the timing of EORTC QLQ-C30 & EQ-5D to: Assessed following enrollment but prior to dosing on Day 1 and then at every 4th cycle up to 48 weeks, then every 6th cycle until disease progression or treatment is discontinued (whichever occurs later); Synopsis, Secondary Objectives third bullet changed to ≥ 1%.
19 March 2015	Changed the definition of PD-L1 positivity from ≥ 1% to ≥ 5% membranous staining in tumor cells and increased the minimum of PD-L1 positive subjects from 58 to 70. Reduced the Creatinine Clearance (CrCl) threshold in the inclusion criteria from ≥ 40 mL/min to ≥ 30 mL/min. Other items have been updated such as; the medical monitor, SAE reporting timeframes and collection timeframes, statistical considerations regarding sample size, and general protocol clarifications.
26 August 2015	Added Objective Response Rate (ORR) as a co-primary objective. Extended subject enrollment in Japan. Other items have been updated such as the medical monitor, statistical considerations regarding the PD-L1 tumor expression and extended enrollment in Japan, and general protocol clarifications.
22 February 2016	Clarified that subjects in Japan, who started treatment after last patient first treatment date of subjects who were enrolled before closure of global enrollment, will not be included in the efficacy analysis. Additionally, other items have been updated, change to the study's Medical Monitor, new fax number for the Study Director, correction to a footnote in table 5.6.2.6-1.
30 September 2016	Provided reference to the newly-updated Investigator Brochure, Version 15.0 in order to ensure the latest safety information is available. Updated Inclusion Criteria contraception requirements. Dose delay criteria updated to add clarification that if treatment is delayed > 6 weeks from the last dose, the subject must be permanently discontinued from study therapy. dose delay criteria concerning drug-related Creatinine, AST, ALT and/or Total bilirubin abnormalities is changed to require dose delay for subject with Grade 2 and discontinuation with Grade ≥ 3 abnormalities regardless baseline. Criteria to Resume Treatment is changed concerning drug-related AST, ALT and/or total bilirubin abnormalities to allow subject with Grade 2 to resume dose when the values return to baseline and management with corticosteroids, if needed, is complete. Discontinuation Criteria is changed concerning drug related AST, ALT and/or Total bilirubin abnormalities to require that subject with Grade ≥ 3 abnormality or concurrent AST/ALT >3 x ULN and total bilirubin > 2 x ULN should be permanently discontinued. Safety Assessment is changed to clarify requirements on physical examination at visits. Management Algorithms is changed to provide latest guidance per the latest version of the Nivolumab IB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported